TUMORS of the LUNGS and MEDIASTINUM

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231 Black and White Illustrations
4 in Color on 2 Plates

LEA & FEBIGER

Philadelphia 1958

Library of Congress Card Catalog Number 58-13560

Printed in the United States of America

To

The Memory of

EVARTS A. GRAHAM, M.D.

MASTER SURGEON – SCIENTIST – INVESTIGATOR

Preface

The subject matter of this volume (i.e., tumors of the lungs and the mediastinum) has been my concern since the early nineteen twenties when I performed my first autopsy on a patient who had died of cancer of the lung in a sanatorium for consumptives. The patient had been referred to the institution by eminent physicians who had arrived at the diagnosis of tuberculosis only after prolonged observation and study. At the sanatorium too the diagnosis (made by a distinguished internist) was "fibroid tuberculosis." Yet the history, the clinical picture, and the x-ray film (which is kept in my files) revealed that it was a typical case of cancer of the lung. The records of the sanatorium disclosed several similarly misdiagnosed cases.

In retrospect, it appears that cancer of the lung was then probably not much better understood than in Trousseau's time (quoted on page 123). There were but few references on the subject in American medical literature and the disease was regarded as a greater rarity. It is noteworthy that as recently as 1930, when an article was published on the high incidence of cerebral metastases from cancer of the lungs, the findings were considered incredible even by the late James Ewing, who wrote a letter questioning the validity of the figures.

In the early nineteen thirties it became clear that cancer of the lungs is a disease with an incidence, in the male, almost equal to that of cancer of the stomach.

The late Evarts A. Graham was one of the first to appreciate the magnitude of the problem and the first to remove in a single stage a lung affected with bronchiogenic cancer. His successful operation thus dramatized the condition and attracted universal attention. Graham's interest in the various aspects of the subject did not abate in the following years. Ultimately (and in the tradition of Joseph Lister), he inaugurated studies on the etiology, i.e., smoking of cigarettes and prevention of the "plague," a work which, among other things, played an immense educational role.

The greater part of this study is devoted to bronchiogenic cancer. Of the material previously published by me on cancer of the lungs but a small portion has been incorporated. The disease is considered from "the cradle to the grave." Particular attention has been drawn to the incipient stages by obtaining records of previous hospital admissions and those of private physicians who had treated the patients at an earlier period. The problem of metastases is discussed in some detail because

of the significance of metastases in the treatment and prognosis of cancer of the lungs (as it is no doubt in cancer of other organs) Moreover a metastasis is frequently misdiagnosed as the primary disease (neoplastic or degenerative) while the pulmonary cancer is overlooked Considerable space is devoted to adenoma of the bronchus (a "new disease") and to mesothelioma of the pleura (an "old disease") Rare or allegedly rare tumors of the lungs are discussed The possible role of environmental factors and of cigarette smoking in the etiology of lung cancer is considered in detail

The second section of this book is concerned with tumors and cysts of the mediastinum which are so often confused with primary and metastatic tumors These tumors are much more frequently encountered than physicians would have us believe Progress in roentgenological technique (detailed by Dr Arnold L Bachman in Chapter 9) made their clinical diagnosis possible They are no longer a *noli me tangere* to the surgeon

The problem of tumors of the chest has broadened in recent years so that their study is no longer a one man job It was thought desirable to enlist the aid of physicians prominent in their respective fields Their contributions are gratefully acknowledged

It has been stated by Claude Bernard that in reports on medical or biological problems it is fallacious to claim completeness The author of this book makes no such claims

New York N Y

B M Fried

Acknowledgements

I gratefully acknowledge permission to use illustrations contributed by

Dr Thomas H Burford and Dr Thomas B Ferguson
Figures 223, 225, 226 227, 228, 229

Dr Richard M Friedenberg
Figures 72*A* and 72*B*

Dr Rafaele Lattes
Figures 163 and 168*B*

Dr Herbert C Maier
Figure 144

Dr Irving Sarot
Figures 157 and 162

Dr Louis Schneider
Figure 230

Dr Israel Steinberg
Figures 166 and 167

Dr Arthur Purdy Stout
Figure 213

My special thanks to Mr Alfred Sundel for his editorial assistance

Mrs Beatrice Salzman has given generously of her time and talents in the preparation of the manuscript For her invaluable assistance I am deeply indebted

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Adenoma and Cylindroma

RARE TUMORS

TUMORS of the LUNGS

Unlike cancer which has arisen primarily in the lung, a cancer that has metastasized to the lung from other organs rarely invades the bronchial wall, and only very rarely causes ulceration of the bronchial mucosa It may, however, occasionally compress the bronchial wall from

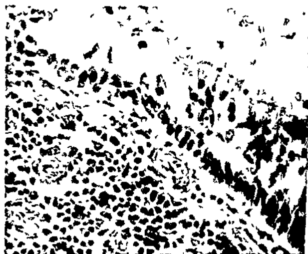


Fig 1 —The lining of bronchial mucosa by basal cells



Fig 2 —Hyperplasia of the basal cells of the bronchial mucosa

without and narrow its lumen, producing an extrinsic bronchostenosis The bronchial origin of the cancer is especially demonstrative in the preinvasive phases or when the cancer is still *in situ*

Basal Cells—Metaplasia —The bronchial mucosa is made up of three types of cells—ciliated columnar, goblet, and basal The last type (Figs

1 and 2) lies close to the basement membrane and possesses features which become active in the inflammatory and regenerative processes of the lungs and bronchi When normal epithelium of the bronchial mucosa is either damaged or destroyed, the basal cells differentiate into columnar cells and "repave the bronchus In fibrogenic conditions of the lungs they often proliferate in excess, sprout out into the surrounding tissue, and penetrate the air sacs They often move deeply into the pulmonary parenchyma, forming nodules erroneously regarded as neoplastic

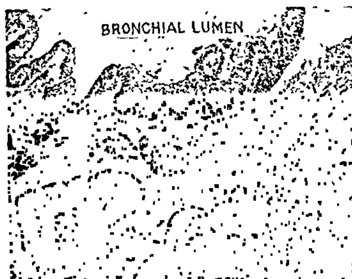


Fig 3—Metaplasia of bronchial epithelium Squamous-cell cancer beneath the mucosa

Since stratified squamous epithelium normally does not exist in the lungs, its presence in diseased lungs was erroneously attributed to the ciliated columnar epithelium, said to have undergone a squamous metaplasia However, on close scrutiny it became apparent that the basal cells (singularly active in regenerative processes of the lungs), and not the ciliated columnar, are the ones which undergo metaplastic transformation Under physiological conditions they differentiate into the normal lining cells of the bronchial mucosa, while under pathological conditions they differentiate into stratified squamous epithelium, which replaces the normal columnar cells The metaplastic epithelium may remain so indefinitely or, under suitable stimuli, evolve into cancer (Figs 3 and 4)

The term "carcinoma *in situ*" (also called "intra epithelial carcinoma") has been applied to the incipient stage of bronchial cancer, during which

the malignant process is confined to the mucosa, limited by an intact (noninvaded) basement membrane (Figs 5 and 6) The malignant nature of the process is evidenced by the proliferating basal cells and by changes in the cells, which proceed to show anaplasia, hyperchromatism, polynucleosis, mitotic activity, disparity in the size, shape, and staining



Fig 4 —Metaplasia of bronchial epithelium with transformation into cancer

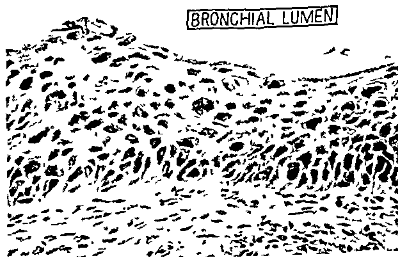


Fig 5 —Cancer of the bronchus *in situ*

quality of the nuclei and loss of orientation It is believed that this is the usual mode or origin of bronchiogenic carcinoma

oma *in situ*

e presence

denotes a

multicentric origin of pulmonary cancer awaits further investigations



Fig 6 —Cancer of the bronchus *in situ*

"ALVEOLAR CELL" CANCER

Another source given for the genesis of pulmonary cancer is said to lie outside the bronchi namely in the so called respiratory epithelium The tumor was therefore termed "alveolar cell cancer" and its identification was based on the following criteria

1 Absence of cancer in the bronchial wall

2 The lining of normal alveolar walls by uninterrupted rows of cuboidal or columnar cells sometimes secreting mucous

3 The uniformity of the histological pattern throughout a lobe or a lung

This has led to the theory of the multicentric origin of cancer the belief that the cancer arises synchronously in a multiplicity of places possibly throughout the lung

Such tumors have been classified as (1) nodular in which the new growth is said to consist of diffusely scattered nodules and (2) massive

in which the new growth is claimed to form a massive or lobar block Subsequently it had to be acknowledged that the "massive" variety resulted from a fusion of the nodules

In fact, the whole concept of "alveolar-cell" origin of pulmonary cancer has been contested on the following grounds.

The failure to detect a cancer in the bronchus with the naked eye does not negate its presence there, for it has been repeatedly observed that widespread metastases may take place in the presence of cancers which



Fig 7—Metastases to both lungs from cancer of the pancreas

cannot be discovered *Minute testicular cancers often yield massive intra abdominal lymph node metastases, small gastric cancers provide voluminous hepatic metastases and barely visible pigmented moles exhibit metastases throughout the entire body Malignant teratomas are of particular interest in this respect* In the past when such a tumor was found in the mediastinal space, it was invariably diagnosed as a primary mediastinal neoplasm, whereas now it is generally regarded as metastatic from the testicle, where the growth vanishes after an extensive seeding, leaving only a scar

There are two possible sources for the so called "alveolar-cell" cancer it may be a metastasis to the lung from (1) an undetected abdominal cancer (Figs 7, 8, and 9), or (2) from cancer of the bronchus which was overlooked or misdiagnosed (Figs 10 and 11)



Fig 8



Fig 9

Fig 8—Lining of the septa by metastatic cancer cell resembling the so-called alveolar cell cancer Biopsy obtained at thoracotomy

Fig 9—Same as in Fig 8 The normal state of the septa must be noticed The neoplastic cells are mucous producing



Fig 10—Primary cancer of the pancreas The similarity of these cells with the metastatic cell (in the lungs) must be noticed

Metastatic Origin—Abdominal cancers which produced pulmonary metastases of the "alveolar cell" type have been frequently observed. Cancers of the thyroid and the gallbladders have yielded similar patterns of metastases (Mitchel Herbut). The following case illustrates an instance in which a "silent" pancreatic cancer produced clinical and anatomic pictures of an "alveolar cell" cancer.



Fig 11—Metastatic (pancreatic) cancer in the lung. The normal septa are lined by the mucous producing cancer cells from the pancreatic cancer showing a picture of a so called alveolar cell cancer.

Illustrative Case

Case 1. *Onset of illness with nonproductive cough, a chill and a brief episode of fever. Gradual development of dyspnea and ... infiltration of ... cal of tissue ... Autopsy findings of carcinoma of the tail of the pancreas with metastases in the lungs.*

History—The patient, a 50-year old female, was admitted to the Lebanon Hospital, New York City, with a complaint of shortness of breath and vomiting. Both her parents had been diabetics. Her mother had died of a cardiovascular disease. At the age of 14 the patient suffered from a "severe anemia" of an unknown nature which lasted for one year. At the age of 31 she had an

appendectomy at 45 a cholecystectomy, and at 46 a hysterec tomy Her menstrual history was normal until the removal of the uterus She had one child who is in good health The woman was born in America and never visited a foreign country So far as she knew she never had any contact with sheep birds or rabbits

In the early part of 1950 she visited Colorado for several weeks and when she returned to New York in April she complained of a nonproductive hacking cough In May she had chills followed by an episode of fever which lasted for 5 days It was diagnosed as a virus infection

In July of the same year she complained of shortness of breath on minimal exertion with simultaneous vomiting The dyspnea increased progressively in severity She became moderately anor exic lost some weight and felt weak

When she was admitted to the hospital she showed a moderate cyanosis of the lips The bases of both lungs showed dullness and rales were audible anteriorly and posteriorly Pleural rubs were felt in many areas Examination of the heart was negative Her blood pressure was 130 systolic and 90 diastolic The liver and spleen were not palpable A rectal examination was negative Her temperature was 100° F her pulse was 96 per minute and her respiration was 22 per minute The laboratory findings were noncontributory The sedimentation rate was 28 mm per hour The tuberculin test was positive in a dilution of 1 to 10 000 and the serological and cutaneous tests for histoplasmin and coccidiodin were negative

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ou X ray
examination of the gastrointestinal tract and the gallbladder was negative and no disease was found in the kidneys or the thyroid The electrocardiogram showed no cardiac abnormali ties and the sputum was negative for tubercle bacilli and fungi The Papanicolaou test was inconclusive

Except for dyspnea and cyanosis which increased steadily in intensity thus requiring oxygen the patient's condition remained unchanged Repeated roentgenological examinations failed to show changes in the chest, and intensive treatment with antibiotics did not lead to any improvement in the clinical status

An exploratory thoracotomy was made with excision of pulmo nary tissue for diagnostic purposes At the exploration the right lung was found to be free from adhesions All lobes contained scattered rubbery nodulations unlike those observed in carcinoma A portion of the right upper lobe was resected The histological diagnosis was pulmonary adenomatosis (Figs 8 and 9)

The dyspnea grew in intensity The patient became restless apprehensive and in constant need of oxygen Signs of right heart

failure appeared with pulmonary edema and cyanosis Her temperature rose and she died in respiratory failure

At autopsy a mucous cell carcinoma of the tail of the pancreas was found (Fig 10) The tail of the pancreas was replaced by a stony hard mass which encroached upon the splenic vessels The peripancreatic and neighboring retroperitoneal lymph nodes contained tumor There were extensive metastases to both lungs (Figs 7 and 11) the parietal pleura the liver and the regional lymph nodes The lungs weighed 2 325 gm The visceral pleura showed many adhesions and the interlobar fissures were obliterated The lungs were firm and coarsely nodulated (Fig 7) On its cut surface the pulmonary parenchyma was diffusely studded with numerous whitish glistening slightly raised nodules which had a tendency to fuse into large masses A considerable amount of mucous was obtained on the scraping knife

The diagnosis was primary carcinoma of the pancreas with metastases to regional lymph nodes liver lungs and pleura Histologically the tumor was made up of tall columnar mucous producing cells lining the alveolar walls which appeared quasi normal (Figs 8 9 and 11)

Comment—Illustrated above is a cancer with all the traits characteristic of "alveolar cell" cancer The autopsy findings of a pancreatic cancer which provided pulmonary metastases of the "alveolar cell" type were a surprise to both the clinician and the pathologist

It is conjectured that the pancreatic cancer reached the lungs via the thoracic duct right heart and pulmonary arteries The neoplastic cells passed the walls of the septal capillaries and adhered to the alveolar walls which they utilized as a supporting substance They spread from one alveolus to another via the pores of Kohn It is even possible that the invasions of the lungs from the pancreas occurred synchronously in a multiplicity of places leading to a multifocal neoplastic proliferation which gave the erroneous impression of a primary multicentric origin of the cancer in the lungs

Bronchiolar Origin—The "alveolar cell" type of cancer may also be produced by a cancer which arises in the bronchus as demonstrated in Figures 12 and 13 This case concerns a cancer of undeniably bronchial origin *Now it has been demonstrated* that the "alveolar cell" type of cancer originates at the periphery of the lung from a bronchiole and it has therefore been defined as bronchiolar or bronchiologenic cancer It invades the respiratory portion of the lung by continuity spreading along the walls of the air sacs

From a detailed study Lumsden reached the conclusion that "The view that spread (of cancer of the lung) occurred by way of alveoli was amply confirmed Spread along the lumina of the air passages was mainly confined to the alveolar walls" Peterson Hunter and Sneeden

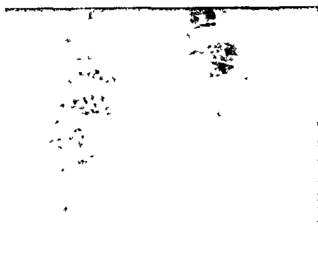


Fig 12—Primary cancer of the left lung with metastases to the right lung



Fig 13—The histological structure of the bronchiogenic cancer shown in Fig 12

Fig 14.—Showing a pulmonary alveolus with scattered phagocytic cells alongside the septa. No epithelial cells can be demonstrated



Fig 15.—A segment from a pulmonary alveolus (in a case of cancer of the lung) lined by histiocytic cells. The similarity between the sessile and the free intra alveolar cells must be noticed

studied five minute pulmonary neoplasms which they accidentally found during an autopsy. They stated: "Evidence as far as obtainable favors bronchial epithelium rather than alveolar cells. Although very small, all (cancers) gave evidence of an ability to invade bronchial walls and to



Fig. 16.—An alveolus from a cat's lung after the intratracheal injection of cod liver oil. The cells alongside the septum are typical macrophages as are the cells in the lumen of the air sac. For comparison, a macrophage from the spleen is inserted in the *right lower corner of the figure.*

spread into the air alveoli." In 1948 I wrote: "The cells in diffuse intra-alveolar (alveolar cell) cancer should be looked upon as a widely distributed canalicular metastasis from an invisible (with the naked eye)

or overlooked cancer of the bronchus . . . The (cancer) cells found lining the septa are not aboriginal but are imported from the bronchioles"

Additional evidence that the 'alveolar-cell' type cancer does not in fact originate from the alveolar epithelial cells was provided by the disclosure that the pulmonary alveoli are lined not by epithelial cells at all, but rather by cells of mesenchymal origin,† which cannot produce an epithelial malignant disease (Figs 14, 15, and 16).

ADENOMATOSIS

The "alveolar-cell' type of cancer has often been linked with a disease termed "adenomatosis" found in man and the lower animals This disease is characterized clinically by (1) a cough productive of a mucoid sputum, (2) steady loss of weight, (3) low grade fever, (4) anorexia, and (5) progressive dyspnea

Roentgenological examination shows multiple soft mottlings or wide areas of consolidation scattered throughout both lungs Postmortem findings correspond to the x-ray picture, revealing diffuse nodulations or a lobar consolidation resembling gray hepatization in lobar pneumonia The bronchi are normal and the pleural cavities are patent The lymph nodes and the visceral organs show no abnormalities Microscopically, the alveoli show the walls lined by nonciliated, mucous-producing, columnar or cuboidal epithelial cells, often forming papillary projections The cells appear normal, and the septa show only slight if any changes

Pathogenesis —The disease known as adenomatosis or *jaagsiekte*, which affects sheep predominantly, is epizootic in Iceland At one time it was regarded as malignant, and the name carcinosis was suggested (Bonne) However, the consensus of opinion is that it is caused by a virus and is contagious, although it could not be transmitted from one animal to another, or from an animal to man Dungal pointed out that in Iceland, where it is epizootic among sheep, it has not been contracted by shepherds who are in constant contact with the animals Wood and Pierson performed a lobectomy on a man for cavities in the right lower lobe, and what grossly seemed to be disseminated miliary tuberculosis proved histologically to be adenomatosis Their efforts to demonstrate a virus in the removed lobe and in the lung at autopsy failed Although quasi-similar histologically, the pathogenic identity of epizootic adenomatosis (*jaagsiekte*) and human adenomatosis has not been demonstrated

The resemblance between adenomatosis in man and "alveolar cell' carcinoma is also only histological In both conditions the walls of the pulmonary alveoli are lined by rows of cells However, while in "alveolar-cell' cancer the cells are malignant, in adenomatosis they are benign

†Fried, B M The structure of the respiratory (terminal) portion of the lungs A M A Arch Int Med 98 691, 1956

In epizootic adenomatosis the epithelial cells of the terminal bronchioles are in all likelihood affected by the unknown pathogen or virus Under

tion of a systemic disease

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Chapter 2

Classification

MACROSCOPIC

In the past clinicians classified pulmonary cancer on one particular phase of the disease (usually on the basis of one roentgenological film) and pathologists classified the cancer from postmortem findings. The pathologists' classification gave no inkling as to the natural history of the disease, and the clinicians' classification portrayed but one particular episode. The dynamic nature of cancer in general and of bronchiogenic cancer in particular, made these methods of classification obsolete. The site of origin of the disease is considered to be of much greater diagnostic and prognostic significance. However, this aspect has not as yet been fully explored.



Fig 17



Fig 18

Fig 17.—Squamous cell cancer of the right middle lobe with no metastases. Accidental post mortem finding.

Fig 18.—Squamous-cell cancer spreading from the right hilus. Metastatic to lymph nodes, liver, kidneys, adrenals and bones.

Probably no segment of the bronchial tree is immune to the development of cancer, but the following areas have been found to be sites of predilection (1) The hilus or the center of the lung (2) the midlung, *i e*, the midzone of the lung, and (3) the peripheral zone where the so called peripheral cancer arises in a secondary bronchus or in a bronchiole close to the surface of the lung

Fig 19

Fig 20

Fig 19—A sharply circumscribed squamous cell cancer of the left hilus with the first manifestations caused by a metastasis to the brain

Fig 20—Squamous cell cancer of the left hilus with lymphangiotic spread toward the parenchyma Death 2 years after onset of respiratory symptoms No clinical evidence of metastases

1 *The central or hilus type (Figs 17 and 18)* which in most instances is a squamous cell cancer arises in the mucosa main bronchus, or in one of its primary divisions 2 to 4 cm belo ina From the mucosa it extends to the lamina ropria It tl s toward the bronchial lumen infiltrat chial wall, s the pulmonary parenchyma It has n ascertai malignant cells remain *in situ* before a sive proc

In appearance cancer of the lung varies in no way from cancer of

within and without the bronchus and invades the bronchial and occasionally the tracheal wall

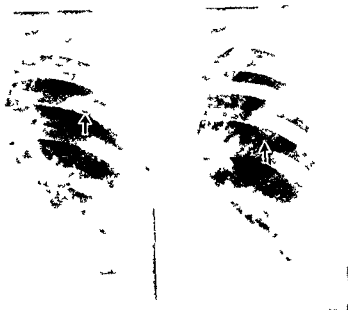


Fig 21 Fig 22

Fig 21 —M lzon (minute) cancer of the lung

Fig 22 —Same cancer 6 months later

The central or hilus type often assumes a massive or lobar aspect Generally the molding of the growth depends in all likelihood on intrinsic (biological) properties and no doubt also on circulatory and environmental factors and durability The slow-growing tumors have a tendency to degenerate in the center crumble and produce central cavities which become infected and often putrid Further the central type can be seen with the bronchoscope at an early period and is soon apt to provide neoplastic cells in the expectoration as well as in the bronchial washings From the clinical point of view this type begins to manifest itself much earlier than the peripherally located bronchial or bronchiolar cancers

2 *The midzone type (Figs 21 and 22)* originates from the cells of the small bronchial branches beyond the mouths of the segmental branches The following describes a case of this type

Illustrative Case

Case 2 History A male patient 72 years of age had been treated for asthma in the out patient clinic for 10 years About 2 years before his death an annular shadow 4 cm in diameter was noticed in his right lung and he was referred to the thoracic clinic with a diagnosis of tuberculosis However the sputum was

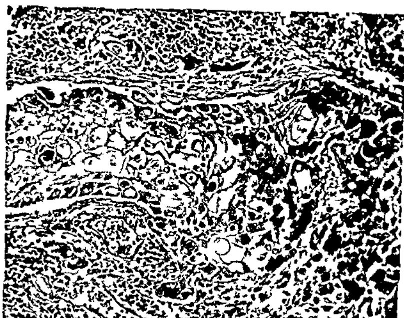


Fig 23—The histology of the cancer (i e squamous cell) shown in Fig 22

repeatedly negative for tubercle bacilli Moreover on *x* ray examination no evidence of tuberculosis could be detected in other parts of the same lung or in the contralateral lung He was discharged fror ... serv ce
for
in t
and clinical data were against the diagnosis of tuberculosis During a routine *x* ray examination of the chest a dense area measuring about 0 5 cm *in diameter was disclosed in the left lung* (Fig 21) The possibility of a cancer was considered but in view of the patient s general condition a bronchoscopy or thoracotomy

were contraindicated Within the next 6 months the size of the lesion in the ... visible as a roughly ro... ... arply de lineated from ... The pa tient's complaints remained unchanged, i e, they referred mainly to his asthmatic condition and to the urinary disturbance He died 6 months following the disclosure of the small tumor in the left lung The tumor was a well differentiated squamous cell cancer (Fig 23) It did not metastasize



Fig 24—Peripheral adenocarcinoma with no metastases in a male of 63 a heavy cigarette smoker since adolescence Posteroanterior and lateral views

3 *The peripheral type (Figs 24 and 25)* finds its origin in the mucosa of a tertiary bronchus or a bronchiole remote from the root of the lung In its early stages the lesion may be round or have a nondescript shape and may be an adenocarcinoma or a squamous cell cancer (Fig 26)

"Coin" Lesion—The solitary (coin shaped) round opaque area observed in the periphery of the lung which hitherto had always been considered a metastasis from a visceral cancer, was discovered to include primary and metastatic neoplasms as well as granulomas From Table 1 it can be seen that only about 30 per cent of cases are cancers (usually

peripheral) while the remaining are tuberculomas, fungus disease histoplasmosis adenomas of the bronchus, and possibly other diseases not as yet identifiable As a rule, the lesion is located peripherally in the upper as well as the lower lobes of the right or left lung

In the absence of signs of cancer in other parts of the body (breast, kidney) a solitary "coin lesion in the lung is a baffling problem which can rarely be solved by clinical and roentgenological means alone Un



FIG 25—Peripheral adenocarcinoma of left lung discovered on an incidental roentgenological examination (Patient hospitalized for congestive heart failure) Posteroanterior and lateral views No clinical evidence of metastases

Table 1 Incidence of Malignant Solitary Round ("Coin) Lesions

	No of Cases	*Malignant*	*Per Cent*
Mahon and Forsee	55	4	7.3
Effler Blades and Mark	24	4	16 6
Storey Grand and Rothman	40	7	17 5
Hutsfeldt and Carlson	33	7	21 2
Sharp and Kinsella	55	15	27 3
Fine	30	10	33 3
O Brien Tuttle and Ferkaney	21	9	42 9
Harrington	16	7	43 8
Davis and Kepsel	67	37	55 0
Total	341	100	29 3

hindered the coin shaped density (if cancerous) grows larger often without changing its spherical shape It is usually discovered incidentally during an x ray examination

Apical Cancer — Another variety of the peripheral type is the apical cancer, which arises at the extreme apex of the lung beneath the dome of the pleura (Fig 27) It originates in the mucosa of a small bronchiole



Fig 26 — Peripheral squamous-cell carcinoma of right lung Pneumonectomy Patient well 6 years after operation

and is often embedded in dense connective tissue (*i e* in a scar) In the incipient stages the lesion is seen as a dense area at the pulmonary outlet and is interpreted as a healed tuberculosis or a thickened pleura (Fig 28) In its progress upward it impinges on the brachial plexus compresses and ultimately invades it thus producing the "brachial plexus syndrome" (A separate section will be devoted to this syndrome) As a rule the cancer is made up of squamous cells but it is occasionally an adenocarcinoma as illustrated in Figure 38



FIG 27.—Mucocellular adenocarcinoma of apex of right lung producing brachial plexus syndrome The histology of the tumor is shown in Fig 38

The clavicle and the upper ribs are usually the first to show metastatic invasion. The tumor has a tendency to cross the median line and invade the contralateral lung as well as the thoracic vertebrae, which causes compression of the spinal cord.



Fig. 28.—Squamous cell carcinoma of left apex producing the brachial plexus syndrome. Clinical diagnosis: apical tuberculosis or thickened pleura.

MICROSCOPIC

In Chapter 1 it was shown that the basal cells of the bronchial mucosa are in all likelihood the sole source of cancer of the lung and that the various cellular types and patterns encountered in primary carcinoma of the lung results from the differentiation of these cells. The following differentiations seem to predominate:

1. Squamous epithelial
   (*a*) keratinizing (*b*) nonkeratinizing
2. Adenocarcinoma
   (*a*) simple (*b*) papillary (*c*) mucocellular
3. Undifferentiated
   (*a*) oat cell (*b*) round cell

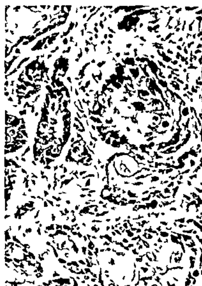


Fig 29



Fig 30

Fig 29—Squamous cell cancer of bronchus with pearl formation

Fig 30—Squamous cell cancer forming rosette like structures



Fig 31



Fig 32

Fig 31—Squamous cell cancer made up of giant cells with bizarre nuclei

Fig 32—Squamous cell cancer with multinucleated giant cells

1 *The squamous cell cancer (Figs 29–34)*, found in about 70 per cent of cases, is the most pleomorphic The variations concern the cellular morphology as well as the groupings of the cells The metastasizing propensity of the squamous cell cancer has often been underestimated With few exceptions it metastasizes to the lymph nodes and distant organs As with the other types, the duration of the premetastatic phase remains unknown However, it is true that it metastasizes much less frequently to the brain and the bones than does the adenocarcinoma



Fig 33

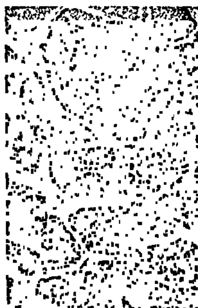


Fig 34

Fig 33 —Squamous-cell cancer of the bronchus made up of clear cells Generalized pulmonary osteoarthropathy

Fig 34 —Undifferentiated squamous-cell carcinoma arranged in nests separated by a fine connective tissue stroma

The prevalence of squamous cell cancer—particularly its incidence in the male which is much higher than in the female—has been linked with the habit of smoking, *i e*, the carcinogen present in tobacco

intrinsic (*i e* biological) factors are no doubt also at play

In the majority of cases the cancer arises in the stem bronchus or in



Fig 29



Fig 30

Fig 29—Squamous cell cancer of bronchus with pearl formation

Fig 30—Squamous cell cancer forming rosette like structures



Fig 31



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Fig 33



Fig 34

Fig 33—Squamous-cell cancer of the lung is made up of clear cells (Centralized pulmonary osteoarthropathy)

Fig 34—Undifferentiated squamous-cell carcinoma arranged in nests separated by a fine connective tissue stroma

The prevalence of squamous cell cancer—particularly its incidence in the male which is much higher than in the female—has been linked with the habit of smoking *i e* the carcinogen present in tobacco

In the majority of cases the cancer arises in the stem bronchus or in

one of the main branches, but it may also find its origin in a smaller bronchus or in a bronchiole, thus producing a midlung or a peripheral cancer

The squamous cell cancer usually produces massive tumors which degenerate in the center in about 10 per cent of cases and form cavities that resemble acute or chronic lung abscesses This type too yields the pneumonia like pattern in which the alveoli are filled with neoplastic cells similar to the cellular exudate in lobar pneumonia In some instances the walls of the air sacs show virtually no changes while in others they become thick and fibrosed



Fig 35



Fig 36

Fig 35 —Undifferentiated round cell carcinoma of the bronchus

Fig 36 —Unclassifiable squamous cell (?) carcinoma of the bronchus

The manner in which the air sacs become flooded with neoplastic cells is not understood Some observers believe that the cancer cells penetrate the alveoli by the aspiration of tumor cells broken off the main growth (aspirational or aerogenous metastasis) others state that the cells reach the air sacs by way of the blood stream through the septal capillaries

It is worth noting that a similar picture is occasionally encountered in cases of extrapulmonary cancer Indeed the process in the lung is at times so extensive as to suggest a blood borne rather than an aspirational metastasis

2 *Adenocarcinoma (Figs 37 and 38)* usually starts at the periphery of the lung and is made up of cuboidal or columnar cells that form acini The acini may be composed of one or two rows of cells sometimes forming papillary projections, *i e* , a papillary adenocarcinoma In a large per



Fig 37 —Papillary adenocarcinoma with a pattern of a so called alveolar-cell cancer



Fig 38 —Mucocellular adenocarcinoma of the upper lobe with a pattern of a so-called alveolar cell cancer

centage of cases the cells secrete mucous In its early stages the tumor is seen as a single nodule which may persist throughout the course of the illness however, in most instances it produces a multiplicity of nodules which fuse and form a compact lobar growth The papillary growth is apparently more malignant than the simple

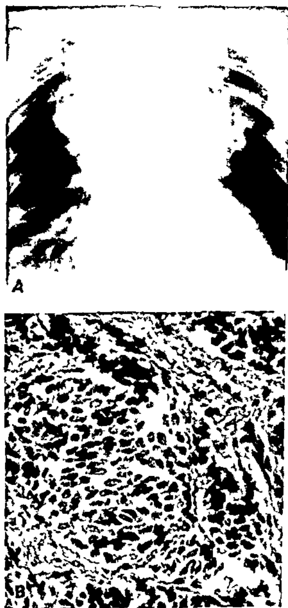


Fig 39.—Oat cell cancer of the lung A x ray film showing the mediastinal location of the tumor B the histological structure of the cancer

Of interest is the predominance of adenocarcinoma in the female in whom it occurs in about one-third of all cases of cancer of the lung whereas in the male only one sixth are adenocarcinomas As stated above, biological (intrinsic) factors rather than extrinsic factors (*e g*, smoking) are probably at play

Adenocarcinoma has often been distinguished from terminal bronchiolar carcinoma (erroneously termed "alveolar cell" cancer) in that adenocarcinoma is said to form a stroma of its own whereas terminal bronchiolar carcinoma utilizes the alveolar septa as its stroma This however is not always the case A terminal bronchiolar cancer like other types often produces a characteristic stroma which resembles the walls of the air sacs

3 *Undifferentiated* These are of two kinds (*a*) oat cell (Fig 39) and (*b*) round cell (Fig 35) The oat cell cancer is remarkably monomorphic The cells are uniform in size and shape resembling grains of oats The growth is usually massive with a scant stroma and the cells have a tendency to form rosette like structures The tumor metastasizes vigorously particularly to the bones and liver but rarely to the brain The round-cell cancer (Fig 35) as the term implies is composed of small round cells with a narrow rim of cytoplasm and dense stained nuclei There is virtually no stroma and the packed neoplastic cells resemble a lymphocytic exudate This type is rarely encountered I have observed three cases in which such cancer was combined with tuberculosis of the lung

The unclassifiable group consists of tumors made up of cells which vary in morphology and which have no specific pattern The tumors tend to become massive or lobar and in most cases show widespread metastases They are most likely a variety of the squamous epithelial cell cancer (Fig 36)

COMMENT

The microscopic or macroscopic classification of primary carcinoma of the lung has not yet provided dependable criteria applicable to prognosis or treatment In the matter of radiation therapy for example the concept and the methods as well as the results have remained virtually unchanged for the past 25 years In the surgical treatment too what progress has been made is due essentially to improved technical methods rather than to better understanding of the morphological character of the cells or of the patterns of the tumor

It has been said that in primary carcinoma of the lung the various types encountered depend upon the differences in the etiology Different types of primary epithelial lung tumors" wrote Kreyberg "show special biological properties indicating differences in the etiology and develop

ment" The British investigator Doll and his associates wrote as follows "In man a close relationship was found between the daily amount smoked and the development of squamous cell carcinoma, but only a slight, if any, relationship with the development of other histological types, primary adenocarcinomas and bronchiolar carcinomas The results accord closely with those obtained in a Norwegian series (by Kreyberg) and they support the hypothesis that histological types of tumors in the same anatomical site may have a different etiology, a hypothesis which is also supported of other sources" This interesting statement, too, is as yet conjectural It is of interest to note the findings of the pathologists that cancer of the lung is frequently composed of two types, namely, adenocarcinoma and squamous cell cancer Liebow (and others) included in his classification a "mixed type" of cancer, *i e*, a cancer composed of two patterns Are there two different etiological agents for the same cancer?

It has been generally demonstrated that squamous cell cancer occurs with much greater frequency in men than in women, and that adeno carcinoma is found much more often in women than in men This has been attributed to various environmental factors and to the effects of cigarette smoking It has been stated that males develop squamous cell cancer because of their smoking habits, while women—generally nonsmokers—are affected mostly by adenocarcinoma (Tar or its products, which are believed responsible for the carcinogenic action of tobacco, induce squamous cell cancers in mice)

The literature has continuously stressed the role of exogenous factors in the genesis of primary carcinoma of the lung, almost to the exclusion of endogenous factors The latter are suggested, however, by (among other things) observations that, cancer of the lung generally could not be induced in mice by the use of carcinogenic agents, although such agents usually caused cancer at other sites in the experimental animals

There seems to be no sustained connection between the degree of cellular differentiation and the tendency to metastasize It has been found that anaplastic types remain confined to the lungs, whereas the differentiated types metastasize Likewise, the opinion that the squamous cell type is usually "infiltrating and relatively nonmetastasizing" has been accepted with reservation

AGE

Bronchiogenic cancer, like cancer of other organs, is predominantly a disease occurring in middle age and after. In 4,307 cases compiled by Ochsner and DeBakey from the literature 1,093 (25 4 per cent) occurred between the ages of 40 and 49 1,470 (34 1 per cent) between the ages of 50 and 59 and 861 (20 per cent) between the ages of 60 and 69

However, the incidence of cancer of the bronchus in younger persons, and even in children, has been reported (Table 2)

Table 2. Age Incidence of Bronchiogenic Cancer

	Number of Cases	
Age	*Males*	*Females*
30–34	6	4
35–39	6	4
40–44	12	13
45–49	23	5
50–54	39	11
55–59	53	7
60–64	43	7
65–69	41	9
70–74	13	5
75–79	8	2
80–84	3	2
85–90	3	0
Total	250	69

SITE

The right lung is more often involved than the left Of 4,732 cases collected from the literature by Ochsner, 2,761 (58 3 per cent) were located in the right lung, and 1,971 (41 7 per cent) in the left Moersch and Tinney found 241 cancers in the right lung, and 122 in the left In cases I have studied, 57 3 per cent were found on the right side, and 42 7 per cent on the left

RACE AND SEX

The incidence of bronchiogenic cancer among the Negro population of America has been the subject of several studies At the Cook County Hospital, Chicago, of 135 patients with cancer of the lung, only 9 per cent were Negro, although Negroes constituted approximately 30 per cent of all patients Rosedale and McKay found 51 white and 6 Negro patients at the Buffalo City Hospital, and according to these observers, the figures correspond to the population division of the two races in Buffalo

At Hines Hospital Illinois Stein and Joslin found 154 white and 10 Negro patients Of the 100 patients who died of bronchiogenic cancer at the Johns Hopkins Hospital and Baltimore City Hospital, 68 were

white and 32 Negro There were 62 white males and 6 white females, 26 Negro males and 6 Negro females (King and Ford).

Halpert, Tripoli, and Holland studied cases from Charity Hospital, New Orleans In the total autopsy material involving lung cancer there were 5,635 males (2,610 white and 3,025 Negro), and 3,227 females (1,228 white and 1,999 Negro), a percentage of almost 2 to 1 in terms of sex Bronchiogenic cancer was found in 123 men (73 white and 50 Negro), and in 12 women (8 white and 4 Negro), a proportion of about 10 to 1

Tripoli and Holland have reported that, during a 20½ year period, 576,810 patients over 12 years of age were admitted to Charity Hospital in New Orleans, 321,709 of whom were white (157,189 male and 146,087 female) The race incidence of 195 patients with bronchiogenic cancer, as given by these authors, is shown in Table 3

Table 3 Race Incidence of Bronchiogenic Cancer at the Charity Hospital, New Orleans

White	130	White males	116
Negro	65	White females	14
Males	171	Negro males	55
Females	4	Negro females	10

From this table it will be seen that of the 195 cases of pulmonary carcinoma, 130 occurred in white patients (116 males and 14 females), and 65 in Negro patients (55 males, 10 females) The incidence of pulmonary carcinoma in white patients at Charity Hospital, New Orleans, is thus more than twice that in Negroes

At the University of Texas Medical School, during a period of 30 years, a total of 5,264 necropsies were performed on white and Negro persons over 20 years of age In this series there were 929 cases of malignant tumors, an incidence of 17 6 per cent Death generally resulted from the tumor, however, in a few cases the cancer was an incidental finding at autopsy Whereas 45 5 per cent of the persons autopsied were Negroes, only 37 8 per cent of the cancers were found in Negroes Male subjects accounted for 68 7 per cent of the total autopsies, but 69 9 per cent of the cancers were found in men Of the autopsies on men, 59 3 per cent were made on white men, but 65 3 per cent of the male subjects with cancer were white While white women accounted for only 43 3 per cent of the autopsies on women, they had 55 per cent of the cancers detected in women Thus cancer was more frequent in whites than in Negroes

In a review of 8,575 cases from the available literature, Ochsner and DeBakey found that 78 9 per cent were males and 21 1 per cent were females The incidence of the disease in the two sexes, respectively, is

shown in Table 4. The comparison by sex shows that bronchiogenic cancer is more prevalent in the male.

Table 4. *Sex Incidence of Bronchiogenic Carcinoma*

Authors	*Number of Cases*	*Males*	*Females*
		per cent	*per cent*
Craver	175	90.30	9.70
Dick	121	82.60	17.40
Fried	319	78.37	21.63
Halbert	135	91.10	9.90
Moersch and Tinney	448	82.60	17.40
Moses	287	70.00	30.00
Palazzo and Mazzei	100	90.00	10.00
Shick	138	84.00	16.00
Steiner	126	79.37	20.63
Tripolt and Holland	195	80.70	19.30
Total	2047	82.90	17.10

Table 5. *Nomenclature of Segments*

Right Lung		*Left Lung*		
Lobes	*Segments*	*Lobes*		*Segments*
Upper	Apical	Upper	Upper Division	Apical Posterior
	Posterior			Anterior
	Anterior			
Middle	Lateral		Lower Lingular Division	Superior
	Medial			Inferior
Lower	Superior			Superior
	Medial Basal			Anterior-Medial Basal
	Anterior Basal			Lateral Basal
	Posterior Basal			Posterior Basal
	Lateral Basal			

Bronchopulmonary Segments.—The customary classification of lung cancer into upper lobe cancer, middle lobe cancer and lower lobe cancer has become rather obsolete in connection with the newly adopted partition of the lungs into bronchopulmonary segments.

The universally accepted division of the lungs into lobes was based on the pulmonary fissures: the right lung with 2 interlobar fissures was divided into 3 lobes, and the left with 1 fissure into 2 lobes. It was deemed more useful to divide the lungs into smaller units or segments, based upon the branching of the bronchi. Each segment whose bound

aries can be delineated by intrabronchial injection of colored gelatin has its own bronchial and vascular component They are separated by a relatively avascular plane In all, 18 segments are identified, 10 in the right lung and 8 in the left The nomenclature corresponds to the *branching of the bronchial tree as shown in Table 5*

The division of the lungs into 18 segments instead of 5 lobes facilitates localization of a lesion In the event of surgical intervention this reduces the resection of pulmonary tissue to a minimum The segmental division is of great importance in inflammatory diseases of the lungs (abscess tuberculosis bronchiectasis) but has a limited application in cancer of the lung where less than a lobe is not removed

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Chapter 3

Etiology

THE intense interest evinced in cancer of the lung is due to its prevalence as well as to its alleged abrupt appearance The high incidence is universally admitted but the statement that it is a *new disease* which has emerged as a result of newly created factors is disputed The view was expressed that the immense rise in cancer of the lung registered in the past decades is in all likelihood more apparent than real Partisans of this view based their opinion on the following premises

1 Cancer of the lung had not been diagnosed by clinicians of the past century because they lacked the diagnostic resources used by modern physicians such as the roentgen rays and the bronchoscope which are essential prerequisites for arriving at a diagnosis These procedures as is well known have been introduced in the clinic since the beginning of the century which coincides with the emergence of the disease

2 From Laennec (1781–1826) to Roentgen (1845–1923) the diagnosis of pulmonary diseases had been based on percussion and auscultation alone Today these methods are considered entirely inadequate

3 Until the discovery of the tubercle bacillus by Koch in 1882 virtually every disease of the lungs characterized by cough expectoration and wasting—particularly if blood had been expectorated—had been attributed to consumption and patients were left to their own fate (My first patients with cancer of the lung observed in the early twenties came from an institution for consumptives)

4 Because of the lack of interest on the part of the clinician patients with cancer of the lung rarely received postmortem examination Then too the number of pathological institutes in Europe as well as in America was very limited there were few competent pathologists and microscopic studies of tissues were infrequently practiced Even at the autopsy table primary cancer of the lung was considered metastatic because of the paucity of knowledge that the neoplasm arises in the bronchus The erroneous dogma enounced by Virchow that organs which are frequently a target for metastases (the liver and the lungs) are only very rarely the sites of primary tumors had been uncritically accepted They swore by the word of the Teacher—*in verbo magistri jurare*

5 Of particular significance is the vast increase of longevity in persons over 60 and 65 (*i e* in individuals of cancer age) in the past decades

From 1900 to 1950 the number of persons over 65 has almost quintupled (Figs 40, 41, and 42)

6 There is a multiplicity of other factors (*a*) a rise in the economic and cultural status of the population seeking medical advice, (*b*) facilities in hospitalization, (*c*) enhanced interest in the disease, and (*d*) improved methods of therapy According to the view of these observers, it is very likely that, with the recent trends of quasi-universal health examinations, the disease will continue to rise for some time to come

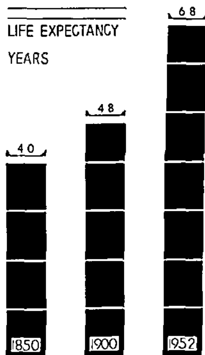


Fig 40 —Life expectancy in 1850 1900 and 1952

7 These observers, too, cite cancer of the prostate as a case in point There were only 83 cases of prostatic cancer reported in the literature up to 1899 (Creevy) Recent statistics tell us that carcinoma of the prostate gland occurs in from 15 to 20 per cent of men over the age of 40 Huggins attributed 5 per cent of all deaths in men past 50 to carcinoma of the prostate Observers do not hesitate to attribute the striking increase to modern methods of diagnosis, and also to increased longevity

8 The emergence of benign pulmonary tumors, *e g*, adenoma, and "rare tumors, is cited as still another case in point These tumors, which were unknown to clinicians and pathologists of the 19th century, also

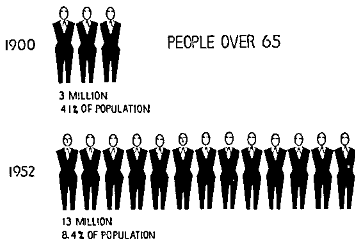


Fig 41.—People over 65 in 1900 and 1952

THE PERCENT INCIDENCE OF PEOPLE OVER 65
1850 – 1950

26 27 30 34 39 41 43 47 54 68 77

1850 1860 1870 1880 1890 1900 1910 1920 1930 1940 1950

Fig 42.—The percent incidence of people over 65—1850 to 1950

have appeared rather suddenly and are encountered with relative frequency due no doubt to newly applied methods of diagnosis

These views have been challenged by *other investigators who have* contended that the above mentioned factors were not alone sufficient to account for the "epidemic" proportions of the increase In white males pulmonary cancer rose from about 0 7 per cent per 100 000 in 1914 to 4 6 per cent in 1933 and to 22 per cent in 1952 In white females it rose from about 0 6 per cent in 1914 to 2 3 per cent in 1933 and to 4 4 per cent in 1952 The number of deaths from pulmonary cancer in *the United States amounted to 3 410 in 1933 to 21 582 in 1952* and to 25 000 in 1954

The opinion seems to prevail that the mounting incidence is real progressive and ever accelerating

Causes —The reason for the emergence and steady rise has been attributed to the extensive industrialization inaugurated at the turn of the century It has been conjectured that the newly developed industries dealing with various physical and chemical agents many of *them* containing cancer producing factors affect the lungs of persons engaged in these industries (occupational cancer) as well as those who inhale the air polluted with the carcinogens (environmental cancer) *

That certain occupations are apt to provoke cancer had always been surmised but Percival Pott was the first to produce convincing evidence to this effect in 1770 He showed that the scrotal cancer which occurred *in men of middle age or in older men was the outcome of the occupation* as chimney sweepers in their teenage years It took 150 years to demonstrate experimentally that tar was the agent responsible for scrotal cancer

CARCINOGENICITY OF TAR AND DERIVATIVES

Yamagiwa and Itchikawa (1918) by painting rabbits ears with tar induced cancers at the sites of application The ear of the rabbit has never been observed to develop cancer spontaneously Since then tar has been applied successfully in the causation of cancer of other organs or structures in different animals with mice being used most often The customary technique consisted in the application (painting) of tar to several cutaneous areas the applications being spaced at short intervals Under the microscope the skin showed excessive regeneration (papillomatous growths) which often but not always culminated in epithelial malignant disease

TAR INDUCED CANCER OF THE LUNG

Moller while studying the rodents left in the laboratory by his late chief Fibiger accidentally discovered that they were affected with

*The terms occupational and environmental are used interchangeably

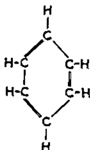
cancer of the lung He found that the animals whose skin had been painted with tar developed cancer of the lung instead of cancer of the skin where the chemical had been applied The experiments were repeated and were corroborated by Murphy and Sturm and by Shabad Murphy and Sturm conjectured that the tar merely lowered the resistance of the animals while the cancer was caused by the inhalation of dust and other "irritating" substances Shabad excised the areas to which the tar had been applied before the appearance of skin cancer which did not prevent the rodents from developing pulmonary cancer In all likelihood the carcinogenic agent applied to the skin with the tar entered the systemic circulation and was retained in the lungs where it induced the malignant disease The experiments are of interest in demonstrating that pulmonary cancer may be induced by the application of a carcinogenic agent to an area outside the lung They are also of interest in connection with the chimney sweepers cancer In both the laboratory animals and the sweepers the carcinogenic substance had been applied to the skin yet in the animals it resulted in cancer of the lung while in the chimney sweepers it produced a cutaneous cancer There is no doubt that in the chimney sweepers the carcinogen reached the lungs via the systemic circulation as well as by inhalation

It may not be amiss to give here the results of the following experiment Tar as said above does not induce cancer in all animals subjected to tarring In many the papilloma (which always follows painting) regresses and in many others it becomes arrested However if the animal with an arrested papilloma is infected with a virus via the blood stream the papilloma begins to grow and becomes cancerous

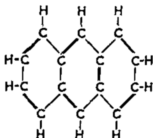
TAR COMPOUNDS

Kennaway Cook and their associates demonstrated that the fundamental compound of many tars is anthracene which is made up of 3 benzene nuclei (Fig 43A B C) By the addition of a benzene ring to anthracene in 1 2 position one obtains 1 2 bezanthracene By adding a benzene ring to 1 2 bezanthracene in the 5 6 position 1 2 5 6 bezanthracene is obtained (Fig 43D, E) Pyrene is made up of 4 benzene nuclei (Fig 43F) while 3 4 benzpyrene is formed by adding a fifth benzene nucleus in the 3 4 position (Fig 43G) The last named is one of the most active carcinogenic hydrocarbons Another powerful carcinogenic hydrocarbon is found in the methylcholanthrene a derivative of 1 2 bezanthracene (Fig 43H)

The isolated and synthetized carcinogenic hydrocarbons are crystals or powders soluble in oils fats or benzol respectively They are administered in solution subcutaneously intravenously intraperitoneally orally or as in the case of tar they are painted on the skin With the dose



A



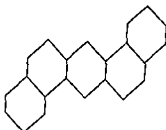
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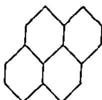
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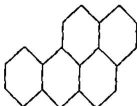
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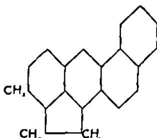
E



F



G



H

cleus
1 2
acene
four
benzene nuclei G, 3 4 benzpyrene made up by adding a fifth benzene nucleus in
the 3 4 position *H* methylcholanthrene a derivative of 1 2 benzanthracene

currently employed methylcholanthrene (chemically closely related to bile acids) and cholanthrene require about 4 months and 1 2 5 6 dibenzanthracene about 7 months for the development of a tumor in a mouse the animal chosen for the experiment

Experimental Lung Cancer—By use of these and other substances pulmonary *tumors* could be induced in mice almost at will In strain A mice (which are normally susceptible to pulmonary tumors) tumors of the lungs were induced in 90 per cent of the animals within 4 months by intratracheal injection of 0 1 mg of 1 2 5 6 dibenzanthracene or methylcholanthrene By using the intravenous route pulmonary tumors developed in 100 per cent of mice of the same strain A (Andervont)

The experimental studies have disclosed a host of interesting data which have revealed that the murine tumor is a neoplasm *sui generis* and is not related to cancer of the lung in man Some of these findings may be briefly restated

1 It has been established that tumors can be produced in the lungs of mice by a variety of substances such as polycyclic hydrocarbons azo dyes nitrogen and sulfur mustard roentgen rays and uretane The last a water soluble substance causes tumors in the lungs only

2 A tumor of the lung can be produced following the administration of the carcinogen at a variety of sites *e g* subcutaneously intraperitoneally or orally In other words a tumor may arise at a distance from the site of application of the carcinogen

3 A lung tumor can be produced with greater ease in animals naturally predisposed to the development of the disease than in those that are naturally resistant which implies that a hereditary factor plays an important role

4 A lung tumor may arise after a brief exposure to the carcinogen In occupational human cancer the exposure is usually protracted over years and there is a long interval between exposure and the development of cancer

5 The tumor agent can be transmitted via the placenta If uretane is administered to a pregnant mouse and the offspring is removed from the uterus one hour later it will develop a pulmonary tumor later in life

6 Pieces of lung from susceptible and resistant inbred strains have been implanted subcutaneously into F 1 hybrids derived from the strains When a carcinogen is administered to the hybrids tumors develop in the lung tissue transplanted from the susceptible strains but not in the tissue from the resistant strain

7 Embryonic lung tissue from half term mice was impregnated with

tory mice turned cancerous. When a single crystal of methylcholanthrene was used for the impregnation an epidermoid carcinoma appeared within 30 to 40 days that was metastatic, transferable and heterologously transplantable. It differed, however, from human cancer in the abundance of keratinization (Green).

In view of the ease with which cancer could be produced by the use of embryonic pulmonary tissue impregnated with a verified carcinogen (methylcholanthrene), Green employed the impregnation method to test other allegedly carcinogenic substances. Thus, instead of the polycyclic hydrocarbon, he impregnated embryonic lung tissue with asbestos, beryllium and various products of tobacco. Numerous experiments and *protracted observation failed to disclose cancers in the experimental animals.* In other words, the carcinogenic properties of the substances mentioned above could not be demonstrated.

The histogenesis of the murine pulmonary tumors remains unsolved. Some believe that they originate in the alveolar cells, others say in the bronchial epithelium, and still others claim to have traced them to both *the alveolar cells and the epithelial bronchial cells.* As stated, in man primary cancer of the lung originates from the cells which line the bronchial mucosa.

Grossly, too, human and murine pulmonary tumors are dissimilar. Cancer of the lung in man originates in one point (unicentric) in the center, midzone or periphery of the lung, whereas in mice the tumor arises synchronously in a multiplicity of places (multicentric), preferably subpleurally. The tumor usually is scattered throughout both pulmonary fields.

In summary, the consensus of opinion is that human and murine cancer are biologically different diseases. Pulmonary cancers of mice have as yet failed to shed light on the etiology of cancer of the lung in man.

LUNG CANCER IN THE HUMAN

Some observers view cancer of the lung as part of the problem of malignant disease and consider that its etiology will not be solved until the final solution of the whole problem is at hand. Others regard it as a problem in itself, intimately *linked with the modern era of industrialization.*

I have quoted (p. 57) the work of Pott concerning the etiological relationship between cancer of the scrotal skin and occupation (environment). Examples of occupational cancer have since been multiplied. Cancer of the bladder in the aniline workers and pulmonary cancer in the *Schneeberg miners are of particular interest.*

Aniline Cancer of the Bladder.—It has been observed that workers exposed to 2-Naphthylamine or benzidine develop cancer of the urinary

bladder with considerable frequency. The mortality rate from cancer of the bladder at the beginning of the century was 1.3 to 1.5 per cent of the total deaths from cancer. The present high incidence is the result of the exposure of workers to the chemical.

Cancer of the Lung in Schneeberg Miners.—The high rate of deaths from pulmonary disease among the miners of Schneeberg, Germany, and of Jachymov (Joachimsthal), Czechoslovakia, has been known for centuries. In fact, it goes back as far as the 16th century, at which time it was noted that a great number of miners of the two localities contracted a fatal disease of the lungs after having worked in the mines for some years. In a certain percentage of cases the disease appeared several years after the miners had been in retirement.

The nature of the disease remained obscure until 1879, when the noted pathologist Carl Weigert diagnosed it as lymphosarcoma. However, when the diagnosis was revised in 1922, it was concluded that it was a bronchiogenic carcinoma. Investigation revealed that of the 600 to 700 miners, 32 died annually, and 24, or 75 percent, succumbed to bronchial cancer. It was further ascertained that the percentage of lung tumors for the years 1875–1912 and 1905–1912, respectively, was 41 and 44 per cent. In 1935 Lange found that the percentage was even higher, from 60 to 70 per cent.

The Jáchymov (Joachimsthal) mines, about 30 miles from Schneeberg, also have been known for centuries to yield a high mortality owing to a disease of the lungs. As in Schneeberg, the symptoms of the malady were chronic cough, blood-streaked sputum, pain in the chest, dyspnea, and gradual decline culminating in death. Again, as in Schneeberg, the disease often manifested itself years after the miner had begun to work in the mines and not infrequently years after his retirement.

Despite the short distance between Schneeberg and Jachymov and despite the similarity between the symptoms of the diseases in the miners of the two localities, the pulmonary condition in the Jachymov workers remained unknown until 1929, when Lowy identified the first case as a bronchiogenic cancer. In the following 2 years 18 new cases were found in 25 men that came to autopsy. Those with cancer had been engaged in the Jachymov mines from 14 to 23 years. A number of them had died *anywhere from 1 to 27 years (usually 6 to 9 years) after leaving the* mines. While in Schneeberg the diagnosis, up to 1922, was lymphosarcoma, in Jachymov, up to 1929, it was tuberculosis.

That the pulmonary tumors were etiologically related to the occupation in the mines was apparent from the fact that the population of the same districts not engaged in the mine suffered from bronchial cancer to a much lesser degree. A trait proper to occupational cancer in general, namely, a long "pause" between the initial engagement in the offending trade and the inauguration of the cancer, was likewise characteristic

of the *Bergkrankheit* (as it was called by the miners) in Schneeberg and Jachymov It is also typical that bronchiogenic carcinoma often developed in miners several years (6 to 9) after their retirement This too is distinctive of aniline arsenic and x ray cancers

Since the opening of the mines in the 16th century copper, iron, silver cobalt arsenic, bismuth and nickel has been mined In the latter part of the 19th century pitchblende (used in the manufacture of uranium dyes) was mined especially in Jachymov In 1909 the manufacture of radium was started in Jachymov and from that period to 1925 26 grams of radium element had been produced Curie obtained radium from pitchblende secured at Jachymov

The particular agent responsible for the bronchial cancer in the miners has been the subject of numerous investigations with conflicting results The prevailing opinion however is that it was radon found in abundance in the mines Other factors were suggested as well such as pneumoconiosis produced by the dust arsenic and possibly heredity The mines had been operated for hundreds of years and the miners have always lived an isolated and segregated life frequently intermarrying (inbreeding)

It was conjectured that the radon acts on the lungs not only through inhalation of radium emanation but also by way of absorption through the skin That workers engaged in the radon industry are liable to develop malignant disease by ingestion inhalation of the noxious substance and also possibly through other avenues has been demonstrated in the case of workers at the American Luminous Dial plants where osteogenetic sarcomas were found in 7 women 20 to 30 years of age employed in that industry from 1 to 4 years As the workers customarily pointed the brushes containing the luminous paints by drawing them between their lips it was assumed that ingestion of the substance rather than its inhalation was responsible for the inauguration of the malignant disease of the bones

Why the bones and not other organs were affected has not been fully explained In this respect it is of interest to note that the reason for the scrotal localization of the cancer in the chimney sweepers or of the urinary bladder in aniline workers is not entirely clear for it is known that in the chimney workers not only the scrotum but the entire body is thickly covered by the soot (concentrated pitch) while in the aniline workers the dye penetrates into the body through inhalation as well as by absorption through the skin The kidneys or the ureters have not been known to develop cancer or to be otherwise affected

In all likelihood there exists a susceptibility *sui generis* of different organs and tissues to malignant disease This is apparent in the lower animals Rats for example frequently suffer from sarcoma of the liver which arises in the wall of a *taenia* cyst whereas mice suffering from the

same disease rarely develop sarcoma. Also mammary cancer is very frequent in mice, while rats are susceptible to carcinoma of the uterus yet hardly ever develop cancer of the breast.

Whatever the avenue of entry, it seems reasonably certain that radon was responsible for the cancer of the bronchus in the Schneeberg and Jáchymov miners.*

These observations served as a starting point in the incrimination and search for environmental (occupational) carcinogenic agents which might have been responsible for the sudden appearance and rapid growth of cancer of the lungs.

CHROMATES

Chromates are regarded as carcinogenic for the lungs. Chromium and its compounds are obtained from chromite ore, which is a mixture of iron and chromium oxides. It has a valence of 2, 3 and 6, and forms both chromium salts and chromates.

Chromium and its compounds have been used for the control of corrosion in various types of reticulating water systems, in the manufacture of dry cell batteries, matches, explosives, in fur and leather dyeing, in bleaching of fats and oils, as reagents in the chemical industry, in electroplating of metal parts, as well as in the manufacture of chromium pigments, dye mordants for tanning of hides, aniline dyes, colored crayons, colored paper, colored glass, and many other objects.

The hexavalent compounds, such as sodium dichromate ($Na_2Cr_2O_7$), considered the most active chemically and also the most widely used in industry, are additionally regarded as the most injurious in terms of an occupational health hazard. The compounds are apt to induce systemic intoxication, perforated septum, chrome ulcers, and chrome dermatitis. They act as a corrosive on the skin and mucous membranes of the upper respiratory tract. The most characteristic lesion found in chromium workers consists in ulceration and destruction of the nasal septums. The ulcer is caused by inhalation of mists or dusts containing chromates. In a study of 285 workers in a chromium chemical manufacturing plant, Edmundson found 61 per cent with perforated septums and 69.5 per cent with ulcers or scars from healed ulcers. Cutaneous ulcers are formed when the chrome is introduced under the skin by way of a fissure of the tegument. The ulcer is usually indolent and heals with the formation of a characteristic scar. No case of malignant growth has ever been observed in the ulcerated areas, whether in the active stage or at some future time.

In 1939 Alwens and Jones reported 17 cases of pulmonary cancer found

*It has been suggested that the pulmonary cancer possibly was caused by a combination of several carcinogens, including arsenic.

in workers engaged in a chrome plant in Germany They referred to Lehmann, who reported 2 cases of *chromate-Lungenkrebs* observed in 1911 and 1912, and to single case reports by Kolsch and Teleki No findings of significance have been published since

In America, Kotin stated "While little question exists as to the increased pulmonary-cancer incidence associated with exposure to chromates," no less an authority than Machle wrote *Extensive epidemiologic studies will have to be done before any carcinogenic hazard to handlers of chromate products can be considered as more than suspicious*"

Bistrup examined 724 employees in the chromate-producing industry in Great Britain by mass radiography, and found only one case of cancer of the lung

In Summary —Evidence hitherto adduced that chromates are carcinogenic, *and that they have played a role in the "epidemic" of cancer of the lung*, is unconvincing

ARSENIC

Hutchinson is credited with the first report, in 1888, on arsenical cancer of the skin The development of cancer of the skin in persons exposed to the chemical is preceded by a protracted period of arsenicism The systemic disturbances are superimposed by a patchy melanosis (hyperpigmentation) of the skin dermatitis, and seborrheic keratosis, the last regarded as a precancerous manifestation It also has been observed that, in individuals exposed to arsenic who also suffer from psoriasis *cancer will develop in the psoriatic plaque It is contended that the* cutaneous cancer is caused by ingestion of arsenic and not through *contact Ingested arsenic is deposited in the skin and its appendages*, and is excreted with the urine

Similar to other occupational cancers, arsenical cancer of the skin develops after a prolonged exposure, and even many years after exposure The interval between the exposure and the appearance of cancer varies from 3 to 40 years, an average of 18 years Kennedy stressed *that* arsenical cancer has a special affinity for the fingers and toes— in contrast to tar, pitch, and shale oil—which have a predilection for the scrotal skin the head, and the neck

While the skin has been shown to be susceptible to the carcinogenic action of arsenic, the lungs as yet have not been found to be affected by the chemical

Claims that many other varieties of metallic dusts and fumes—beryllium, copper, lead, iron, mercury—are carcinogenetic have similarly not been borne out on close scrutiny Evidence thus far adduced has turned out to be "conjectural, inadequate or negative"

ASBESTOSIS

Asbestosis is a form of pneumoconiosis caused by the inhalation of asbestos dust The industry involved is engaged in the manufacture of asbestos textile producing insulated mattresses brake linings fireproof curtains and clothing Approximately 20 000 workers are so employed both in this country and Canada

As a rule the disease is tolerated for many years with mild symptoms but occasionally it is serious particularly when complicated by another disease

Asbestos is a hydrate magnesium silicate which gives off a dust in the process of manipulation It consists of fragments of fibers and small particles of rounded or angular shaped needle like dust particles The "needles" vary in size from 10 to120 microns The smaller particles are usually accommodated in the alveoli but the large ones become lodged in the air sacs and terminal bronchioles In the reaction to asbestos dust there occurs a remarkable formation of curious looking golden yellow segmented structures (asbestos bodies) which are probably produced from a substance absorbed by the "needles" and coagulated as a gel The asbestos bodies are slender elongated segmented structures with bulbous ends assuming a dumbbell or a drumstick shape They can be found in smears of sputum as well as in the pulmonary tissue after fixation in formaldehyde

The asbestos dust is phagocytosed by macrophages to a much lesser degree than silica The type of reaction depends on whether the "needles are of a larger or smaller size It usually consists of a production of fibrosis around the terminal bronchioles a thickening of the alveolar septa and the formation of nodulations In the more advanced stages atelectasis and bronchiectasis occur The lungs have a veiled or ground glass appearance generally confined to the lower lobes while the upper lobes show emphysema complicated occasionally by voluminous bullae which at times rupture inducing spontaneous pneumothorax

The concept that asbestosis is carcinogenetic and apt to cause bronchiogenic cancer has dated back to the mid thirties In 1943 Wedler found 14 cases of pulmonary cancer combined with asbestosis in 92 autopsied persons with asbestosis an incidence of 15 per cent In England the Chief Inspector of Factories reported that from 1924 to 1946 the diagnosis of asbestosis was made during life or at autopsy in 226 cases In 31 or in 13 2 per cent of the cases cancer of the lung was found Twenty two of 128 males in this group (17.2 per cent) and 9 of 107 females (8 4 per cent) had pulmonary cancers

In 2 451 autopsies performed at the Queens General Hospital New York City Holleb and Angrist found 401 cases with cancer (16 35 per

cent) of various organs Fifty-nine of these, or 14 71 per cent, were bronchiogenic, and 2 were combined with asbestosis

In 4,137 autopsies performed at Yale Medical School from 1918 to 1938 Homburger found 45, or 1 08 per cent, with *primary cancer of the lungs* During the same period a diagnosis of asbestosis was made 8 times Of the 8 cases, bronchiogenic cancer was found 4 times It is of interest to note that of the 17 cases with silicosis, only 2 cancers were discovered

Cartier, *in a study of 120 patients with asbestosis,* found that 12 had died of pulmonary tuberculosis, 17 of cardiovascular diseases, 2 of bronchopneumonia, 1 of an unknown cause, and 6 of carcinoma of the lung—an incidence of 5 per cent

The role of asbestos in the rise of pulmonary cancer was based on the following

(1) The combination of the two diseases had been found so frequently as to be regarded as etiologically related

(2) A high incidence was found in women—8 4 per cent In Merewether's series of 31 cases, it occurred in 29 per cent, and in Gloyne's series of 17 cases, in 41 per cent

(3) The cancer was usually found in the lower lobes, which is also the seat of choice for asbestosis

It is of interest that in the past 20 years, 60 cases of this combination have been reported by as many as two dozen authors, which is indicative of the rarity of the disease Cartier, who found 7 cases of cancer of the lung in 120 persons who died of asbestosis, stated that he found among the employees in the asbestos industry 7 more patients with pulmonary cancer who did not have asbestosis Moreover, a general survey of all the employees in the industry did not seem to "indicate evidence of a causal relationship"

Data thus far accumulated are insufficient to include asbestos in the class of carcinogenetic agents which played a role in the "epidemic" spread of cancer of the lung

SILICOSIS

When chemically pure silica (SiO_2) dust particles which do not exceed 10 microns in diameter reach the pulmonary alveoli, they provoke a cellular response not unlike that of virulent tubercle bacilli The cells normally found in sparse numbers on and within the walls of the air sacs begin to "swell" in size and number, detach themselves from their sedentary seat, and avidly phagocytose the silicous particles They often gorge themselves to such an extent that their cytoplasms burst from the load as well as from its toxicity The liberated particles are then picked up by newly arrived voracious macrophages, which in turn either succumb from "indigestion" or carry their load to hilus lymph nodes

They also agglomerate *in situ* to become transformed into fibroblasts (densely packed macrophages usually undergo such a metamorphosis) ultimately becoming calcified and hyalinized A "ripe" silicous nodule ordinarily about 6 microns in diameter is thus made up of concentrically arranged dense fibrous and hyalinized tissue with a calcific center and at the periphery fibroblasts lymphocytes and carbon pigment The firm nodules like glass beads are disseminated throughout both pulmonic fields first in relation to the points of division of the bronchial tree and later diffusely In some instances due to superimposed infection or to atelectasis the nodules form massive agglomerations which produce a radiographic shadow imitating bronchiogenic carcinoma The damaged parenchyma carries with it changes in the bronchial tree as evidenced by bronchiolitis obliterans and by bronchiectasis but precancerous changes such as metaplasia or excessive proliferation of epithelial cells are rarely observed

In the opinion of Anderson and Dibble a group of pulmonary cancers

gested primary pulmonary cancer in 3 of them an incidence of 005 per cent Of 1 357 cases studied at the Trudeau Sanatorium at Saranac Lake only 1 case of pulmonary tumor was diagnosed Of the 14 230 cases in which silicosis was not present only 2 presumptive pulmonary tumors were noted

The statistics based on roentgenological evidence was supplemented by necropsies from 3 739 cases collected from the available literature and 178 from their own laboratory There were but 32 cases in the combined series showing primary malignant tumors in the lungs which suggests an average incidence of about 8 per cent They reached the conclusion that inhaled dusts cannot be considered as etiological factors in the development of primary carcinoma of the lung

Kennaway and Kennaway stated that the factors which lead to silicosis appear not to be active in producing cancer of the lung The view of these observers has been universally accepted

AIR BORNE CARCINOGENS

Even if one is to accept that the above enumerated industries provide carcinogens the limited proportion of the population engaged in those industries would not be sufficient to account for the epidemic of pulmonary cancer involving town and country Another possible source was therefore explored namely the air The idea that the air contains cancer inducing substances was based chiefly upon (1) the fact that modern

industrialization is confined essentially to large urban centers and (2) the observation that the epidemic affected the urban population to a greater extent than the country dweller

The suggestion that the sudden emergence of cancer of the lung was possibly due to carcinogens which "hover over the face of the earth" originally was mentioned by continental physicians in the early twenties The Swiss clinician Staehelin and others incriminated tar (used extensively in painting roads) gasoline and other substances used by motor vehicles as probable carcinogens inducing bronchiogenic cancer Mice were exposed to coal tar fumes from the exhausts of automobiles other rodents were painted with tar or gasoline but the experiments were inconclusive or negative The theory was further invalidated by the fact that cancer of the lung showed a rise in countries where tar had not been used for painting roads

To be sure the experiments of yore were rather rudimentary and could not be fully relied on In recent years the following sources were explored (1) vehicular exhausts from gasoline and Diesel engines (2) industrial effluents from varied sources hydrocarbon emissions from petroleum refining and distribution installations (3) effluents from home and commercial incinerators (4) soot and other hydrocarbon emissions secondary to commercial production as well as utilization of carbon blacks coal and petroleum tars (5) metal fumes and dusts from steel Atmospheric samples from the allegedly polluted air were collected tested qualitatively and quantitatively for the presence of carcinogens and the solutions of the extracts were applied to mice by painting their backs in the customary manner The Herculean labor which these investigations have consumed can only be conjectured they cannot be adequately reviewed here Suffice it to say that as yet they have not provided sufficient data to incriminate aerogenous carcinogenic substances in the epidemic" of lung cancer Kotin wrote "It is again suggested as a reasonable possibility that the numerous unanswered questions relative to the causes of the increasing frequency of lung cancer are more capa f the atmosphere rather than not advanced beyond the

BACTERIA

The association of bacteria nematodes and helminths with malignant tumors has been reported on many occasions and the belief was expressed that it was etiological A striking example was produced by Fibiger who attributed the origin of cancer of the cardia of the stomach in rats to a nematode *Gongylonema neoplastica* Another example has been cited in cancer of the urinary bladder in persons infested with

bilharzia (*Schistosomum haematobium*) Similar agents have not been incriminated in the genesis of pulmonary cancer

The Tubercle Bacillus—*Mycobacterium tuberculosis* was probably the only microorganism which had been regarded as carcinogenic for the

became excessive and malignant others believed that the role of the tubercle bacillus was etiological

The concept that Koch's bacillus is etiologically related to cancer of the lung was expressed independently by von Hansemann and by Ewing who stated in virtually identical terms that the "chief etiologic factor of cancer of the lung is tuberculosis" Neither of these pathologists produced clinical epidemiological or experimental evidence

Some observers expressed the opinion that cancer of the lung and pulmonary tuberculosis are antagonistic or mutually exclusive This was not borne out by other observers who found the combination of the two diseases in a considerable number of cases They observed it (1) in the same lung (2) in different lungs (3) in different lobes of the same lung and (4) in the same lobe While in the first three eventualities the association was in all likelihood accidental in the fourth—where the diseases collided in the same lobe—an etiological possibility could not be blankly dismissed To be sure Koch's bacillus is by no means carcinogenic However the malignant disease usually develops in areas of a long standing fibrotic tuberculous lesions In persons with a chronic productive tuberculosis there occurs an active response of tissues by repair *i e* by regeneration of epithelial structures which occasionally undergo a malignant transformation

While the role played by bacteria in carcinogenesis is to all appearances nil that of viruses is apparently of significance

VIRUSES

Virus Tumors—A tumor is considered of viral origin when it can be transmitted from animal to animal by a cell free filtrate or when inoculation is followed by the formation of specific antibodies

The idea that a neoplastic disease may be inaugurated by a virus dates back to the past century but evidence was lacking until 1910 when Rous succeeded in transmitting a tumor (sarcoma) from one chicken to another by a cell free filtrate which was believed to harbor the inciting virus In recent years Rous and his associates have been able to induce cancer in rabbits by injecting acellular solutions obtained by filtrating tumor

tissue through cell tight filtrates, the filtrate presumably containing the virus.

In 1931 Shope found a large number of wild cottontail rabbits in the Middle West affected by small, multiple, papillary fibromata. The apparently benign tumors were transmitted to the wild cottontail rabbit as well as to the domesticated rabbit by inoculating them with tumor tissue (grafts) or with filtrates devoid of cells. It was significant that while the papilloma in the wild rabbit generally pursued a benign course, in a large number of cases it became cancerous in the domesticated rabbit. The animal bearer of the tumor developed specific antibodies which increased with the advance of the growth, and which protected healthy rabbits against inoculation. Similar to viruses, the causative factor possessed an affinity for certain cells (cytotropism), such as the epidermis, producing an epidermoid carcinoma of the skin.

An epithelioma of the rabbit* which could be transmitted from animal to animal by grafts alone (and not by cell-free filtrates), was found to manufacture antibodies which increased in amount with the advance of the tumor. The pathologist Luké ascertained that a carcinoma of the kidney, which he found in the swamp frog, was caused by a virus. A variety of tumors and leukemias in fowl have been demonstrated to be caused by viruses.

The role of a virus in experimental tar cancer was pointed out in recent years. As stated in the early paragraphs of this chapter, the repeated application (painting) of tar to the skin of rabbits leads to excessive proliferation of the epidermis forming papillary outgrowths, which then either develop into cancer or disappear (heal) if the tarring is discontinued. However, if the animal is infected with a virus (*isolated* from the papilloma of Shope), the infection usually concentrates in the area painted with tar, and the arrested and innocuous papillary growth almost abruptly assumes a malignant course, soon appearing as a squamous cell carcinoma.

These and many similar observations have given prominence to the idea that viruses play an outstanding role in carcinogenesis. Indeed, some observers hold the view that viruses are possibly the single factor *causing carcinoma*. They *believe that man* probably contracts or harbors carcinogenic viruses, which act in "cooperation" with hormones, chemical and physical agents, parasites and nematodes, respectively. Rous, an exponent of the virus theory of cancer, believes viruses to be "the nearer cause of cancer . . . the only carcinogenic agent known to produce tumors by *direct* action, for other carcinogenic substances act indirectly by inducing a preliminary chronic inflammation (irritation) which only ultimately undergoes a malignant metamorphosis."

*Named Brown Pearce epithelioma, after the pathologists who first described it.

While in lower animals some spontaneous malignant tumors have been convincingly shown to be caused by viruses in man no instances have as yet been observed None of the traits characteristic of virus carcinoma has ever been noted in bronchogenic cancer

TRAUMA

Two aspects of the etiological relationship between trauma and cancer have been investigated *namely (1) the role of trauma in the initiation* of cancer and (2) the alleged tendency of metastases to settle by predilection in traumatized areas

Trauma as Carcinogen —The literature contains clinical reports which tend to sustain the concept that trauma to an external organ has led to the development of cancer From a legal point of view the problem is of particular significance because of the many litigations involving claims by injured persons seeking compensation on the grounds that the alleged trauma induced cancer The question was dealt with in some detail by Knox and Ewing and recently by Pack In an extensive review Ewing quoted a number of cases in which the relationship between trauma and cancer appeared at first glance to be unassailable but after a competent investigation was disproved The data provided by the patients were usually misleading and it was often possible to ascertain that the tumor arose prior to the traumatic incident "The presence of an unsuspected tumor" wrote Ewing tends to bring about the occurrence of injuries at a tumor bearing area and to intensify the subjective symptoms and local effects of the injuries Ewing defines this phenomenon as traumatic determinism"

In the past sarcoma was attributed to a single traumatic insult and giant cell tumors of the bones were claimed to be caused by injury These assertions have since been refuted It has been demonstrated that such tumors are related to the disturbances in the function of the parathyroid glands Clinical reports claiming that cancer of the lung resulted from a single trauma to the chest could not be sustained Similarly attempts to produce tumor in animals by trauma have not been successful

The suggestion has been made that trauma may play the role of a cocarcinogen It has been shown that when animals treated by a single irritating application of a carcinogen are subsequently subjected to repeated applications of a noncarcinogenic irritant such as croton oil a squamous carcinoma will ensue It has been stated that suboptional exposures to carcinogenic hydrocarbons serve as an initiating phase by converting some of the cells in the skin of experimental animals to a preneoplastic condition Some observers have maintained that following this stage of "precarcinogenesis" or "initiation" nonspecific agents such as wound healing croton oil freezing with carbon dioxide snow

and mechanical irritants play an "augmenting" (cocarcinogenic) role in bringing out neoplasms of the skin It has been surmised that a single trauma may possibly play a similar cocarcinogenic or "augmenting" role

Be that as it may, cases where tumor develops following a trauma should be investigated with the utmost thoroughness It should be determined whether (1) the trauma was authentic and adequate, (2) the part affected by trauma was previously normal, (3) the tumor originated exactly at the point of injury, (4) a reasonable length of time intervened between the injury and the appearance of the tumor, and (5) a positive diagnosis of the nature of the tumor was made Furthermore, a detailed and occupational history of the patient should be taken to determine if cocarcinogenesis might have played a role

Trauma and Metastases.—In Chapter 6 it is stated that metastases have a predilection for some organs or sites Some observers argue that a traumatized area is a point of predilection for metastases

The role of injury in the fixation of bacteria or vital dyes has been noted on various occasions For example, the scarification of the skin of rabbits infected with tubercle bacilli will induce tuberculides at the site of the scarification even though the skin does not normally become infected, not even in the advanced stages of tuberculosis I have also noticed that in rabbits infected with tuberculosis, tubercles will appear at the point where the ear had been pierced by a wire used for the attachment of a tag Similarly, vital dyes (pyrrol blue or trypan blue) injected into animals will concentrate predominantly in an area of inflammation, because of changes in the vascular permeability produced by the inflammatory injury

The role of injury in the localization of metastases has been the subject of experimental investigation Jones and Rous found that the injection of a suspension of mouse tumor into a healthy peritoneal cavity is not, as a rule, as successful in producing metastases as a similar injection into the subcutaneous tissue They found, however, that the resistance of the peritoneal lining can be largely, if not completely, abolished by a preliminary injection of a mechanical irritant They placed kieselguhr, glass rods, or tumor cells in the peritoneum of many mice, and found that there was a considerable tendency of the injected tumor cells to become implanted in the regenerating tissue surrounding the foreign material They believed that the regenerating tissue in the areas of inflammation was more apt than normal healthy tissue to provide a stroma necessary for the implantation of the neoplastic cells Saphir and his associates [illegible] mechanical irritation (i e trauma) on [illegible] with [illegible] carce [illegible] epithelioma) In no instance were they able to find tumor in the areas of irritation

It may be seen that the role of trauma in the localization of metastases remains unsolved It is however, almost universally accepted that a single trauma plays no role in the initiation of cancer or in the localization of metastases

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Chapter 4

Etiology (*Continued*)

SMOKING AND CANCER OF THE LUNG

New Hazards.—There are about 1,600,000 deaths in this country each year. Of these 25,000 or 1.5 per cent of all deaths and 10 per cent of all cancers are due to cancer of the lungs. There are 8 times as many deaths from cancer of the lungs today as there were 20 years ago. According to statistics, no other type of cancer is increasing so fast as lung cancer. Figures compiled by the American Cancer Society show that cancer death rates in general are either leveling off or dropping (Fig. 44).

The rapid rise in the incidence of lung cancer, while the incidence of cancer of other organs remains at a virtual standstill, suggests to many observers that it may be due to the emergence of a new cancer

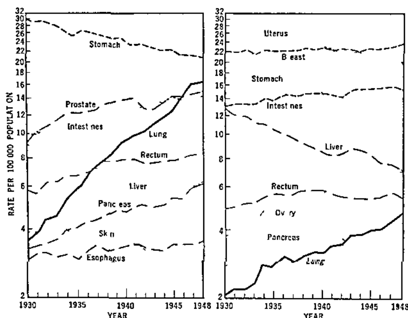


FIG. 44.—Duration of smoking in years: 605 lung cancers in males. (Wynder and Graham, 1950.)

producing agent which predominantly *affects the bronchial mucosa* through inhalation thus inducing the malignant disease of the bronchus

It is almost as though *the population has been exposed to some new* hazards stated Dr Cameron of the American Cancer Society One group of observers considers the "new hazards to lurk in the air (in environmental elements) others consider them to lie in the excessive smoking of cigarettes This latter group believes that the tar (a proven *carcinogen) contained in the inhaled smoke of the tobacco is deposited* on the smoker s bronchial mucosa and ultimately leads to the formation of cancer of that organ (During the past 33 years the number of cigarettes consumed per person in the United States has increased 456 per cent!) Other observers take a middle position believing that the rapidly mounting incidence of lung cancer is due to both environmental *carcinogenic agents and the smoking of cigarettes*

The possible role of environmental factors in initiating cancer of the bronchus has been discussed in the previous chapter The conclusion drawn was that the studies conducted to date have thus far failed to demonstrate a positive link between air carried carcinogens and cancer of the lung Several observers in the past believed that smoking might be the cause of the rapid rise of bronchial cancer but their conclusions did not attract attention because their technique was unconvincing and *the menace of bronchial cancer was not known on the scale it is today*

Flory in order to ascertain whether tobacco smoke contains a carcino genic substance painted the skin of rabbits with tar produced by the *destructive distillation of tobacco In another series of experiments he* applied tar obtained by smoking tobacco in pipes In no instance was he able to induce cancer of the skin in the lower animals Other ob servers (Andervont Green) have failed to produce cancer of the lung *in laboratory animals by the use of the identical* carcinogenic agents which have been used with great success to produce cancer of other organs or structures Shimkin by intratracheal injection of 1 2 5 6 dibezanthracene or methylcholanthrene was able to induce tumors of the lungs in 90 per cent of his animals within four months the tumors were benign adenomatous lesions however which in no way resembled bronchiogenic cancer as observed in man Attempts were made to study *the effect on the lung of intratracheally injected* tar (in dilution) with a view towards producing a cancer But the experiments had to be discontinued because of the gravity of the pulmonary lesions produced by a single injection The lungs are exquisitely sensitive to almost any substance injected by way of the trachea The changes which they show are often difficult to interpret Oils lipids and saprophytic bacteria may induce pulmonary lesions not too dissimilar from those induced by bezanthracene

It has been pointed out that cancer of the *lung* was induced in lower

animals by the application of tar to their *skins* without producing a cutaneous malignant disease These experiments are of importance because they have demonstrated that cancer of the lung can be induced by a carcinogen brought to the lung via the circulatory system Let us remember that chimney sweepers developed cancer of the skin and not of the lungs Yet they no doubt inhaled large quantities of soot over a long period of time

Statistical Data —In order to ascertain a possible link between cancer of the lungs and cigarette smoking Wynder and Graham interrogated a large number of patients with cancer of the lung and another group free from the disease Their study led them to the following conclusions

1 Among those with bronchiogenic cancer (other than adenocarcinoma) 96 5 per cent had been moderately heavy to chain smokers for many years compared with 73 7 per cent among the general male hospital population without cancer

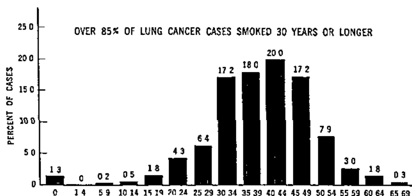


FIG 45 —Progressive increase in deaths due to cancer of the lung in men (*left*) and in women (*right*) while cancer of other organs remained at a standstill (American Cancer Society)

2 The occurrence of carcinoma of the lung in a male nonsmoker or minimal smoker was a rare phenomenon (2 per cent)

3 Of patients with cancer of the lung who had a history of smoking 98 1 per cent had smoked for over 20 years

4 Of all male patients with cancer of the lung 94 1 per cent were found to be cigarette smokers 4 per cent pipe smokers and 3 5 per cent cigar smokers Inhalation among cigarette smokers was believed to be a factor in the increased incidence of the disease (Fig 45)

The studies of Wynder and Graham have been pursued by other observers in America England Germany Holland Finland and Switzer

hand with essentially the same results. Subsequently the studies have been widened and divided into two types: (1) the retrospective type *in which patients with and without lung cancer have been questioned about their previous smoking habits* and the histories thus obtained were compared; (2) the prospective ("forward looking") type based *upon the principle of questioning a large number of people about their* smoking habits and then following their progress for several years.

The individuals in the latter group were divided into heavy, moderate, light, and nonsmokers, *and the causes of death in each of these groups* were subsequently scrutinized. According to Hammond and Horn, the lung cancer death rate of those who never smoked was only 14.0 per 100,000 per year. *Among men with a history of having smoked cigarettes* regularly but not cigars or pipes, the death rate was 141.6 per 100,000 per year *(10 times as high).*

The rates for occasional smokers and for cigar smokers were about the same as for those who never smoked, but pipe smokers had a higher rate *(35.2 per cent).* *Men with mixed smoking habits (cigarettes plus cigars* or pipes) had a lung cancer death rate lower than that for the cigarette-only group but much higher than any of the other groups.

The statisticians of the American Cancer Society affirm that cancer of the lung is about 27 times more frequent among those who smoke 2 packs of cigarettes a day than among those who have never smoked. *Also they state that a man who has smoked heavily for many years* (2 packs or more a day) has about 1 chance in 10 of eventually developing lung cancer; a man who smokes less than a pack a day has about 1 chance in 36 of developing the disease, while the odds for a nonsmoker developing cancer of the lung are about 1 in 270.

Those who Smoke	*Chances of Developing Lung Cancer*
2 packs a day	1 in 10
1 pack a day	1 in 36
none	1 in 270

British investigators too have reached the conclusion that the male mortality from cancer of the lung concerns heavy smokers to a much *greater extent than nonsmokers. Their figures show that the risk of death* from cancer of the lungs is directly proportional to the number of cigarettes smoked. They estimated that approximately 9 per cent of males aged 25 years *who smoked* between 25 and 50 cigarettes a day might be expected to die of lung cancer before they reach the age of 75, i.e., 1 man in 11. In a recent report Wynder stated: *"About 10 per* cent of males more than 25 years of age who smoke in excess of 20 cigarettes a day will develop lung cancer by the age of 75. A person *smoking 40 cigarettes a day is 70 times* as likely to develop lung cancer

as is a nonsmoker The hazard is proportional to the amount of smoking" Wynder believes that 80 per cent of all cancers of the lung would not have occurred but for tobacco smoking

At the Seventh International Cancer Congress held in London in July, 1958 Horn reported the results of a study which he conducted under the auspices of the United States Public Health Service The subjects of his study were 198 926 veterans of the United States Armed forces all of

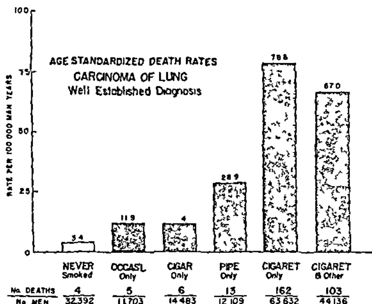


Fig 46—Rates by type of smoking as classified from lifetime history

whom held Government life insurance policies They had served in the armed forces between 1917 and 1940 Almost all were men ranging in age from 30 to 90 years The majority were 50 to 70 years of age The report covered 7,385 deaths during 2½ years (July 1954 through December 1956) From an analysis of 6 203 veterans who were smokers and 1 179 veterans who were nonsmokers Horn reached the conclusion that among regular cigarette smokers lung cancer was the cause of death 9 85 times as often as among nonsmokers" (Figs 46–49) *

Sex Ratio —The low incidence of lung cancer in women as compared with men (a ratio of about 1 to 4) was cited as strong evidence sustaining the etiological relationship between cigarette smoking and cancer of the bronchus The low incidence in women was attributed to the fact that women have not been heavy smokers or that they have been smoking to a much lesser extent than men until recent years However

*Courtesy of the J A M A

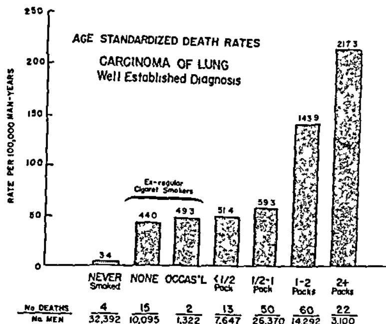


Fig 47 —Rates by current amount of cigarette smoking

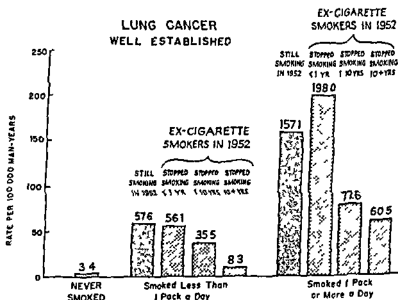


Fig 48 —Rates for nonsmokers, ex smokers and continuing smokers

the incidence of cancer is a complex biological problem which cannot be explained on the basis of exogenous factors alone It is well known that cancer affects both sexes in about equal proportion the difference lying in the affected organs (uterus cervix ovaries) while men on the other hand suffer to a much higher extent from cancer of the lung Cancer of the stomach too occurs with much greater frequency in men than in women (Fig 44)

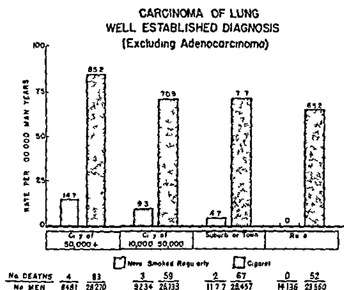


Fig 49 —Urban and rural rates for cigarette smokers and men who never smoked

The low incidence of lung cancer in women as compared with men was recorded in the literature in the early nineteen twenties before the advent of the tobacco problem Of 307 cases culled from the literature and reported by me in 1932 258 occurred in men and 49 in women a ratio of about 5 to 1 In my own 47 cases (also reported in 1932) 39 occurred in men and 8 in women a ratio of about 4 5 to 1 The higher incidence of adenocarcinoma in women as compared with men is also very likely due to endogenous factors the nature of which is not understood and not to a carcinogen brought from the outside

Type of Cancer —The tobacco lung cancer association was also said to be supported by the statistical increase in cases of squamous cell and undifferentiated-cell types of cancer of the lung These types were stated to be caused essentially by the tobacco tar However the squamous cell type of cancer is not invariably produced by tar or its

derivatives Thus the squamous cell cancer of the lung in the Schneeberg and the Joachymstal miners is induced by radon and the squamous cell cancer of the skin which is induced in man and in lower animals by the use of tar is also readily induced by the application of other chemical and physical agents Finally the squamous cell cancer of the uterine cervix is not caused by tar or by its products

It is of interest in this respect to note that the incidence of metastases in cancer of the lung has been found to have greatly increased in comparison with the figures reported 2 or 3 decades ago Since squamous *cell cancer is the type of cancer said to metastasize much less vigorously* than other types the incidence of metastases should have declined There is little doubt that the statistical increase in the squamous cell type of lung cancer (as in the increased incidence of metastases) is due to improved histological diagnosis and not to the tar contained in cigarettes

Synchronous Rise of Lung Cancer and of Cigarette Smoking —Adherents of the cigarette lung cancer association theory state that the rise in the incidence of cancer (which they believe coincided with the increased consumption of cigarettes) started about 3 decades ago and that at present cancer of the lungs occurs in about 10 per cent of all cancers However almost similar figures were reported by German physicians in the early nineteen twenties Berblinger found that in the years from 1919 to 1924 it was observed in Jena in 8 3 per cent of all cancers Wahl reported in 1927 that 7 per cent of all cancers observed in the Moabit Hospital in Berlin over a period of 10 years were of bronchial origin Junghanns found that in Dresden from 1923 to 1927 cancer of the lung occurred in 20 68 per cent of all cancers Kikuth found that during the period from 1889 through 1923 cancer of the lung was observed in 9 5 per cent of all cancers in the Hamburg Eppendorf Municipal Hospital In fact European physicians of that period had already pointed to the high incidence of pulmonary cancer and focused their attention on the possible reasons for its rise

Experimental Data —In order to ascertain whether or not tobacco contains a carcinogenic substance experiments were conducted by Wynder Graham and Croninger on mice painted with cigarette smoke tar obtained from cigarettes puffed down 60 at a time in a *specially constructed* laboratory machine In 71 weeks (one half of the life span of the animals) of tar application to the skin (considered to be equivalent to 30 to 50 years of cigarette smoking in man) 36 of 82 animals (25 females and 11 males) developed cutaneous cancer The experiments demonstrated the presence of a carcinogen in the cigarette smoke capable of inducing skin cancer in a high percentage of animals but they failed to show that the carcinogen is capable of inducing lung cancer in animals Moreover it has been estimated that the amount of carcinogen

present in tobacco is indeed, very small and is unlikely to cause cancer of the lung in man

Summary —The figures compiled by American and British investigators pertaining to the association of cancer of the lung with cigarette smoking show, beyond a doubt, that cancer of the lung occurs with much greater frequency in heavy smokers of cigarettes than in nonsmokers However, the figures have not yielded irrefutable evidence of an etiological relationship between the two The objections raised to this concept are based chiefly on the grounds that the cause of lung cancer (unlike the cause of an acute infectious disease) cannot be ascertained from epidemiological findings only Some observers have suggested that smoke from cigarettes might possibly play a nonspecific promoting or cocarcinogenic role in lung cancer rather than an initiating carcinogenic role (see p 71)

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Chapter 5

Clinical Manifestations

THE clinical manifestations of cancer of the lung should be studied against a background of its protean manifestations. In a large percentage of cases cancer originates in a lung which is the seat of a chronic pneumopathy and in the subsequent development (often in the early stages) it induces changes in the lungs and pleural cavities which may then obscure and overshadow the malignant disease. In 1938 I wrote "Carcinoma of the lung is another masquerading disease. It is masquerading not so much *per se* as by virtue of its complications."

A disease whether of pathogenic or degenerative origin usually passes through a latent or nonapparent phase before it begins to manifest itself. In this respect cancer is no exception. At the onset cancer is confined to a circumscribed area and its manifestations are strictly local. This holds equally true of many other pulmonary diseases. A biological test as it is used in the discovery of latent syphilis is not as yet available for the diagnosis of latent cancer of the viscera.

It is useful to classify the manifestations into two groups: (1) those referred predominantly to the organs of respiration, *i.e.* to the lungs; (2) those referred chiefly to extrapulmonary organs, *i.e.* to the abdominal viscera, the central or peripheral nervous systems, the skeleton, or to a systemic disturbance.

Past History.—In patients with complaints referring to the organs of respiration a history of their previous illnesses, habits and occupations is of great importance.

The habits of the patient, particularly with reference to smoking, should be ascertained. While the etiological relationship between cigarette smoking and cancer of the lung has not as yet been conclusively established, the data at hand are convincing enough to warrant a serious clinical scrutiny in this respect.

The patient's occupation should not be bypassed. That many types of cancer are traceable to occupation (occupational cancer) is no longer doubted. Cancer of the scrotal skin in the chimney sweepers, of the urinary bladder in the anilin dye workers, of the skin in radiologists, and of the lungs in the Schneeberg mine workers, to cite only a few instances, are cases in point. *With the advent of the modern industrial era some* chemical compounds employed in certain trades have been noted to be

carcinogenic for the lungs This aspect is dealt with in greater detail in Chapters 3 and 4

Present Illness—In Chapter 1 the conclusion was drawn that cancer of the lung originates in the bronchus It arises in the mucosa from where it invades the bronchial wall The neoplastic process may primarily affect the main bronchus or one of its branches It may also arise in a bronchiole A cancer is referred to as the "central or "hilus" type when it originates in the vicinity of the pulmonary root or the hilus and as the "peripheral type when the neoplasm originates in the wall of the bronchiole at the periphery of the lung It is generally accepted that in the central type symptoms appear earlier than in the peripheral type because the bronchus is looked upon as the focal point about which early symptoms hinge It is desirable to elaborate on this point in some detail

According to Jackson the bronchi are a living moving labyrinth of resilient tubes enlarging in lumen changing in contour and elongating in inspiration diminishing in lumen and length changing in contour and swaying on expiration In fact the bronchi perform peristaltic movements dilating in inspiration and contracting in expiration The bronchi are not inert thoroughfares for the transport of air but are dynamic structures actively participating in the act of respiration as well as in the defense against the penetration of organic and inorganic matter into the lungs There is no disease of the lungs in which the bronchi remain passive Vice versa there is no disease of the bronchi in which the lungs remain unaffected

As a result of the neoplastic process the bronchial tube in which the tumor has arisen loses its elasticity and dynamism and becomes a rigid structure As a result of the mural infiltration with tumor and the fibroblastic proliferation the bronchial lumen becomes narrower or stenotic The degree of the stenosis depends upon the size of the bronchus (in large bronchi it may be minimal) and also upon the type of tumor Some tumors tend to spread toward the lumen while others tend to advance predominantly toward the wall of the bronchus

1

Pulmonary Manifestations

Emphysema—This process which takes place in the bronchus is reflected promptly in the respiratory portion of the lung supplied by the bronchus There occurs a disturbance in the balance between the two phases of respiration (Fig 50) The expiratory phase which is normally slower than the inspiratory phase assumes a still slower tempo while

the forceful inspiration remains virtually unaffected There occurs a sort of check-valve mechanism whereby, with each inspiration, a portion of the inspired air becomes trapped in the alveoli, producing a segmental or lobar emphysema In some cases the air sacs are so distended as to form bullae which can be demonstrated with the x-rays Auscultation

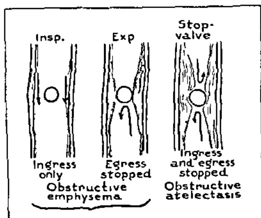


Fig 50—The effect of complete and partial obstruction of the bronchial lumen on the pulmonary parenchyma

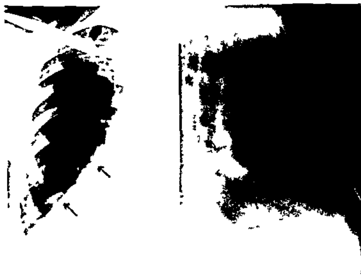


Fig 51—Atelectasis of the right lower lobe caused by bronchial obstruction Posteroanterior and lateral views

(perfunctorily performed by modern day physicians) will reveal diminution or absence of breath sounds in these areas with surrounding zones of hyperresonance and exaggerated breath sounds

Atelectasis —This process too is caused by the stenotic bronchus Here also the impaired function of the bronchus caused by the mural and intraluminal neoplastic invasion brings about a collapse of the pulmonary parenchyma that is generally limited to a segment or to an entire lobe (Fig 51) The main bronchus very rarely is completely obstructed usually it is the branch bronchi or the bronchioles that become occluded The atelectatic area shows suppression of breath sounds over the involved area

PNEUMONITIS

Although a person inhales 12 000 liters of air in 24 hours taking in enormous quantities of particulate matter and bacteria the lungs normally remain free from bacteria This is due (1) to the barrier which the pathogens meet in the bronchial mucosa and (2) to the defensive phagocytic (macrophage) apparatus of the respiratory portion of the lung

The involvement of the bronchus by the neoplastic process affects the respiratory function of the lung as well as the defensive power of the pulmonary parenchyma The lung becomes a ready prey to infection Patients who have been suffering from a pneumopathy (*i e* asthma or chronic "bronchitis) show an exacerbation of their symptoms their cough intensifies and expectoration increases *At times their sputum* contains specks or streaks of blood They develop a kind of relapsing fever accompanied by indisposition and moderate anorexia This phase of the disease is usually neglected by the patient and often "toned down" by the physician who "cures the patient with antibiotics

Episodes of recurrent pneumonitis in a person of middle or past middle age should be thoroughly scrutinized These individuals should promptly undergo a roentgenological examination of the chest and a cytological examination of the sputum

Chronic Pneumonitis —In a person of cancer age a pneumopathy is frequently a challenge There has probably never been a case of cancer of the lung which has not been diagnosed at the outset as *pneumonia* Vice versa pneumopathies in recent years have been mistaken for cancer This holds particularly true of the so called organized pneumonitis The disease is usually localized in the upper part of the lung and is characterized by a persistent cough blood streaked sputum or an obvious hemoptysis pain in the chest and dyspnea The patients complain of anorexia and a steady loss in weight They appear quite ill in general On histological examination the lungs show wide areas of condensation of the pulmonary parenchyma (*i e* fibrosis) and the

bronchi show inflammation and narrowing of the lumina Ackerman and his associates have reported that in 10 of their patients with this condition a diagnosis of cancer was made in 3 of the cases this diagnosis was considered to be the second most likely Some of the patients underwent pneumonectomies for alleged cancer of the lung Indeed it is probably just as important to avoid a false positive diagnosis as it is to avoid a false negative diagnosis (Fig 52)



Fig 52—Chronic organizing pneumonitis misdiagnosed as cancer of lung Pneumonectomy

Lipid Pneumonitis —Lipid pneumonitis is another pneumopathy mistaken for cancer (Fig 53) This type of pneumonitis has been observed in adults who had been given oils or fats for medicinal or nutritive purposes It has also been observed in persons who had been using oil as nasal drops The lipids produce a pneumonitis because they enter the lungs instead of the esophagus When small amounts are used they provoke ephemeral reactions but when a single large dose or repeated small doses of oil are used they lead to an intense reaction that involves sizeable portions of the lung The reaction to vegetable oil is more intense than it is to mineral oil because the former

is less irritating and is disposed of by phagocytosis with greater difficulty

Lipid pneumonitis may also result from an accumulation of endogenous fat in the lungs. The source of the fat has not been fully ascertained but it is surmised that it accumulates as a result of a fatty metamorphosis of the pulmonary parenchyma caused by a low grade inflammation. Fat is observed in bronchopneumonia with infarction in the vicinity of caseous tuberculous foci and in pneumonic areas distal to bronchial carcinoma. Generally it is found in lungs that have chronic



Fig 53 — A lipid granuloma B squamous cell carcinoma

obstructive lesions of the bronchi or the bronchioles. The possibility that the fat reaches the lungs via the circulation should be entertained. The fact that absorbed albumens and carbohydrates pass into the liver while fatty substances are transported to the right side of the heart and lungs by way of the lymphatics and the thoracic duct suggests that the lungs play a role in the metabolism of the lipids. Possibly the lipids are retained in the lungs as a result of a local metabolic disturbance. There they induce a pneumonitis similar to that caused by the exogenous lipids.

The oil brought in from the outside (exogenous) accumulates in the alveoli of the lower lobe (rarely in two lobes of one lung and very rarely



Fig 54 —Carc no na s spect Surg cal disclosure of a l pid granuloma The tomogram shows central excavation of the granulo na

in both lungs) Pneumonitis caused by endogenous lipids is usually bilateral

The pneumonitis induced by lipids as a rule causes a complex reaction because of the fat and the pathogens to which the lung has become prey The histological appearance is essentially that of a long standing partially organized bronchopneumonia with scattered nests of granulocytes lymphocytes and lipophages (macrophages) The lipophages predominate in the earlier stages (Fig 55) On cut surface the lung is golden yellow resilient, and similar to xanthomas In the more advanced stages

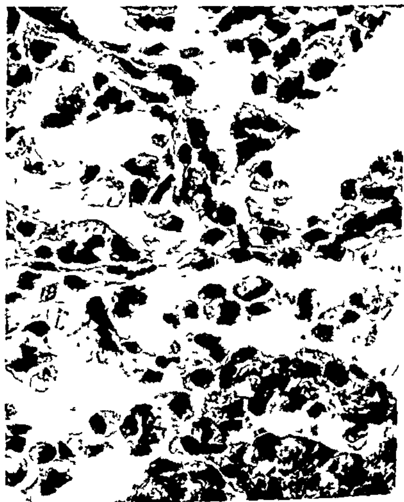


Fig 55 —Early stage of lipid pneumonitis There is an accumulation of macrophages (lipophages) which phagocytize the oil and store it in their cytoplasms (The macrophages originate from the cells of the alveolar walls)

the lung becomes fibrosed shrunken, and firm The term paraffinoma" has been given to "tumors" produced by paraffin oil

In elderly individuals lipid pneumonitis is not rare Volk and his associates found that 57 or 14 6 per cent of 389 chronically ill patients had lipid pneumonitis In most instances the patients used mineral oil as a laxative In many cases oil containing drugs were used as nose drops

is removed

The diagnosis requires clinical acumen and indeed awareness Cyto logical examination of the sputum is often helpful It shows the presence of lipophages with fat droplets in their cytoplasms that are detected with special stains (scharlach R) A biopsy either by a lung puncture or by thoracotomy is sometimes necessary in order to arrive at a correct diagnosis

Cough —Even before the development of pneumopathies the disturbed dynamism of the bronchial tube (as well as the damaged bronchial mucosa) induces an irritation" of the throat attributed to the smoking of cigarettes and a cough productive of a serous seropurulent or muco purulent sputum The cough may be dry brassy spasmodic or hacking and is often predominantly nocturnal Frequently it is merely a sort of grunt disregarded even by apprehensive and observing individuals Coughing is regarded lightly by patient and physician alike because of its usual occurrence in persons of all ages However its appearance in a person of cancer age particularly if accompanied by a low grade fever or by changes in its character should not be dismissed lightly A cyto logical and bacteriological examination of the sputum should be per formed in addition to an x ray examination of the chest

Sputum—Hemoptysis —The sputum—which may be watery mucoid mucopurulent or purulent scant or abundant—is usually not character istic in appearance Enormous amounts of watery sputum are expector ated by patients with terminal bronchiolar cancer While in a few patients the expectoration remains clear throughout the illness in the majority of cases it becomes blood streaked in the early phases of the disease In about 35 per cent there occurs a hemoptysis while in about 17 per cent it is the first symptom Brun found 40 per cent of 626 pa tients to have had hemoptysis Ochsner and DeBakey found hemoptysis as the chief complaint in 19 per cent of cases studied and 48 per cent had had it sometime during the illness

Unlike adenoma of the bronchus in which bleeding is usually copious and frequent in carcinoma the amount of expectorated blood is small perhaps one or two teaspoonfuls Blood streaked sputum and hemoptysis

often accompany bronchiectasis and tuberculosis, but in the diagnosis of individuals of middle or past middle age, cancer should be thought of first

Of 200 cases of hemoptysis investigated by Moersch, 59 occurred in malignant tumors, 53 in bronchiectasis and 11 in pulmonary tuberculosis Abbott and Hopkins found that infiltrating adenoma of the bronchus and bronchiogenic carcinoma were the most frequent causes of hemoptysis Their findings are shown in Table 6

Table 6 Hemoptysis in Diseases of the Lungs

Diseases	*No of cases*	*Per cent*
Adenoma (infiltrating)	7	100 00
Bronchiogenic carcinoma	187	53 60
Lung abscess	65	49 20
Bronchiectasis	239	43 50
Tuberculosis	302	36 50
Fungi	9	33.30
Congenital cysts	19	26 30
Metastatic carcinoma	25	24 00
Mediastinal tumors	70	20 00

It may be seen that adenoma and carcinoma of the lung are the main causes of hemoptysis, followed by bronchiectasis and tuberculosis Hemoptysis also occurs in lipid pneumonitis (rarely), asthma aneurysm of the aorta and pulmonary infarct Copious bleeding was observed in chronic tracheobronchitis and in angioneurotic edema of the lungs Hemoptysis requires a roentgenological, cytobacteriological, and bronchoscopic investigation

Wheeze —A wheezing sound in the chest is heard in a variety of bronchopulmonary diseases All is not asthma that wheezes" stated Jackson The sound is caused by partial obstruction of the bronchial lumen Obstruction may be complete, partial constant or intermittent and may be due to tuberculosis of the bronchus, to a benign or malignant tumor, or to an asthmatic plug of mucous It also may be caused by a lesion compressing the bronchus from without which would lead to a narrowing of the bronchial lumen The left main bronchus may be compressed by (1) various pulmonary or mediastinal lesions (2) an enlargement of the left auricle, or (3) an aneurysm of the left pulmonary artery the arch of the aorta, or the descending aorta The bronchus may finally be compressed and its lumen narrowed by enlarged peribronchial lymph nodes sarcoidosis, and lymphomatoid disease Enlargement of the lymph e root of the lingula induces broncho-

stenosis and atelectasis of the middle lobe or so called middle lobe syndrome

The wheeze caused by partial obstruction of the bronchial lumen can be heard on one side of the chest and is accentuated by forced expiration it is heard best with the patient lying on the affected side and with the examining ear close to the patient s mouth (Fig 56)

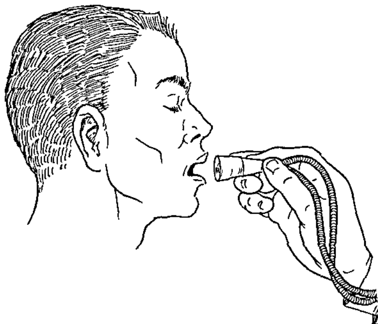


Fig 56—Testing for wheeze

Johnson and his associates in a study of 100 patients who had had bronchoscopic examinations found bronchial obstruction in one half of the cases They observed that among patients with bronchial obstruction the following were commonly found (1) a localized wheeze (2) a cough which had altered in character (3) a local reduction in breath sounds and (4) localized rhonchi When the main bronchus was involved a localized wheeze was perceived in 45 per cent of cases when lobar in 29 per cent and when segmental in 5 per cent The wheeze disappeared when the bronchial occlusions became complete or when the obstructing matter was removed

In any case of a unilateral wheeze bronchoscopic and cytological examinations are quasi mandatory

Stridor.—An obstruction proximal to the bifurcation of the trachea is the cause of stridor. Formerly clinicians considered it pathognomonic of *cancer of the lung*. *It is rarely observed.*

Dyspnea.—It is not so much the size of the tumor as the topography that usually causes dyspnea. This is particularly prone to appear in instances of cancer spreading around the trachea, bronchi or blood vessels which leads to their compression, the narrowing of their lumens and *therefore an interference with circulation and respiration*. Dyspnea is a common complaint of patients with lymphangiotic cancer, which sometimes assumes an asphyxiating aspect. This is discussed in greater detail in Chapter 6. In the presence of small tumors, large and rapidly accumulating pleural effusions cause dyspnea. Severe dyspnea likewise *occurs in atelectasis of the lung due to occlusion of a bronchus or to a* suddenly occurring pneumothorax. Finally, dyspnea is an outstanding feature in the Superior Vena Cava Syndrome.

Hoarseness.—Hoarseness is caused by involvement of the recurrent laryngeal nerve by a tumor which extends to the mediastinum.

The recurrent (inferior) laryngeal nerve, a motor branch of the vagus arises from the latter where it crosses the left side of the aortic arch. It passes below the arch and up on its right or medial side to gain the interval between the trachea and esophagus (Fig. 57).

Unilateral paralysis of the nerve may be produced by mechanical, traumatic, inflammatory and neoplastic processes, the last is by far the commonest. Of 203 cases of unilateral paralysis of the nerve Clerf found that 114 were caused by tumors. Of these 64 were bronchiogenic cancers, 18 esophageal, 11 thyroid and 11 mediastinal metastases from various sources (2 involving the trachea and 8 of a varied group of neoplasms).

Paralysis of the vocal cord due to damage of the left inferior laryngeal nerve is occasionally found in mitral stenosis and in congenital heart disease with dilation of the pulmonary artery, the latter is considered by some investigators to be the principal cause of the injury.

Of particular importance is hoarseness as the first and sole manifestation of bronchiogenic cancer. I have observed patients in whom one sided *laryngeal paralysis* occurred several *months before the appearance* of a roentgenological evidence of a neoplasm in the lung.

The patient whose chest film is shown in Figure 57 had been hoarse for 8 months when he first consulted an internist.

Cyanosis.—*As in instances of dyspnea, the occurrence of cyanosis* will largely depend on the topography of the tumor or on some of its complications and not alone on its size. Thus in some of our cases the bronchus of the right lower lobe was completely blocked and the bronchi of the middle and upper lobes were partially blocked. The patients were dyspneic and orthopneic with a definite asthmatic stridor on expiration

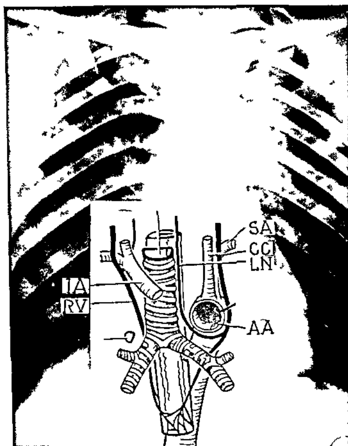


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yet their cyanosis was not a prominent feature One patient whose chief complaint was dyspnea and cyanosis of 6 weeks duration showed a small pulmonary tumor at necropsy There was however a hydrothorax and metastases to the pleura pericardium heart and liver Cyanosis is a prominent feature in Superior Vena Cava Syndrome and in lymph angiotic cancer

Weight —In a considerable number of patients with cancer of the lung the chief complaint is referred to the gastrointestinal tract specifically to the stomach Many observers chanced upon pulmonary cancer while

their patients were being treated for an allegedly digestive ailment These patients have been treated for the "stomach trouble" with special diets, which caused reduction in their weight The pulmonary cancer *per se* does not cause noticeable loss of weight until the disease has reached an advanced stage. A stubborn cough or severe pain in the chest caused by a metastasis often 'kills" the appetite for food, resulting in anemia and loss of weight



FIG 58—Horner s syndrome in a person with cancer of the left apex (Superior pulmonary sulcus tumor)

Cachexia.—Almost every patient with an actively growing cancer displays certain changes in his appearance which experienced physicians frequently discern It is often defined as a 'cachectic hue" Most patients with cancer of the lung, particularly if the disease is protracted, show various degrees of cachexia But one should not expect to find it in the early stages

Horner's Syndrome—This syndrome is characterized by sinking of the eyeball, drooping of the upper lid, slight elevation of the lower lid, constriction of the pupil, narrowing of the palpebral fissure and changes in the vasomotor and sudorific activities of the skin of the face (Fig 58) Horner's syndrome is observed in association with a variety of conditions, such as tumors of the spinal cord, syringomyelia at the level of either

the seventh or eighth cervical or the first thoracic segments of the spinal cord cervical rib it is also observed in apical carcinoma of the lung or in metastatic carcinoma which has invaded the brachial plexus Horner s syndrome will be discussed in greater detail in another section

Pain —Patients with cancer of the lung frequently complain of pain in the chest It is not necessarily caused by an invasion of the pleura or the chest wall by cancer but instead rather often its manifestations are early caused by the stenosing (atelectatic) pneumonitis which implicates the pleura A striking example of pain in cancer of the bronchus is observed in the so called "Superior Pulmonary Sulcus tumors which are provoked by pressure or invasion of the brachial plexus by the apical cancer

Capps demonstrated that the visceral pleura is insensitive to pain and the parietal pleura is sensitive pain is felt in the thoracic wall and alongside that distribution of the intercostal nerve which supplies that particular segment of the pleura

The pulmonary parenchyma like the visceral pleura is insensitive to pain while the bronchi may be the source of painful sensations White and Smithwick stated that pain arising from the larger bronchi is transmitted over somatic vagal afferent axons According to Jackson pain is felt more intensely in the bronchi than in the trachea He rarely heard patients complain of pain during bronchoscopy and still more rarely of pain in the tracheobronchial tree when it contained a foreign body

Morton and his associates found the lining of the trachea and bronchi to be sensitive and painful when the tracheobronchial tree was stimulated electrically during bronchoscopy The pain arising from the bronchial tree was referred to the homolateral anterior chest within 2 to 4 cm of the sternum or to the anterior cervical region 2 cm from the midline Pain in the tracheal region is felt in the midline anteriorly extending from the larynx to the xiphoid process

In cancer of the lung pain in the chest is frequently complained of It varies in intensity from a mere discomfort and paresthesia to an intensely painful sensation that requires sedation and narcotics In the following case the clinical and radiographic pictures were characteristic of pneumonitis However the presence of paresthesia of the back pointed toward the diagnosis of carcinoma invading the chest wall which was borne out by postmortem examination

Illustrative Case

Case 3 History —A male clerk 67 years of age was admitted to the hospital with the complaint of cough productive of a tenaceous sputum occasional hemoptysis pain in the back and loss of weight He had smoked about 20 cigarettes daily for the past 40

years and since adolescence had consumed considerable amounts of alcohol until about 6 years before admittance

About 10 months prior to his admission to Montefiore he was hospitalized elsewhere on complaints of weakness of about 6 months duration a steadily increasing hacking cough productive of a tenaceous yellow sputum and of a gradual loss of weight The physical signs and the roentgenological picture were compatible with the presence of fluid in the left pleural cavity Bronchoscopy showed the lumen of the left lower bronchus reduced to a mere slit and the biopsy showed an inflammatory process but no cancer Thoracentesis yielded pus and a thoracotomy was performed in order to drain the empyema Roentgenological examination of the chest following the removal of the pus showed a large round thick walled cavity confined to the posterior segments of the lower half of the left lower lobe Cultures of the pus yielded pneumococci resistant to penicillin The patient developed intractable pain in the left chest and intermittent hemoptyses

Examination at the Montefiore Hospital showed the lower two thirds of the left thorax to be dull to percussion with absence of breath sounds on auscultation There was a remarkable paresthesia of the skin of the posterior left hemithorax corresponding to the area of the dullness The liver was considerably enlarged and the fingers and toes showed moderate clubbing

Roentgenological examination showed a dense shadow replacing the lower half of the left lung with a translucent area in the

The upper half of the

histological examina

The bone marrow was hypercellular There was an erythroid hyperplasia with marked hypochromia and poikilocytosis The peripheral blood contained 2 500 000 erythrocytes per cubic mm and 5 gm hemoglobin The white blood cells numbered 13 000 per cubic mm and the differential count was normal The blood chemistry was noncontributory

The patient died 3 weeks after admission

At autopsy the entire lower lobe of the left lung was replaced by a cancer with a centrally located cavity 12 by 10 cm in diameter which was filled with necrotic material The new growth invaded the costal pleura and obliterated the pleural cavity Metastases were present in the lymph nodes right adrenal and in the mucosa and submucosa of the stomach The cancer was made up of anaplastic cells

Comment —The case illustrates the difficulties encountered in making a diagnosis of cancer of the lung in the absence of histological proof Had tissue been removed from the wall of the cavity at the time of the

thoracotomy (more than one year before death) and examined under the microscope the course of the illness would have been different the man's life prolonged and agonizing pain avoided

The process of cavitation in pulmonary cancer is an important phenomenon because of its frequent occurrence and also because the excavation resembles a lung abscess with which it has been and still is frequently confused The French clinician Ameuille was the first (in 1923) to report a case of a patient who was referred for surgery with the diagnosis of an abscess of the lung During the thoracotomy Ameuille



Fig 59 —Bronchiogenic cancer of the left lower lobe with cavity formation There is a fluid level

out of curiosity (*par curiosité* as he put it) examined a bit of the removed tissue under the microscope and to his great surprise found that he was dealing with *"cancer pulmonaire a forme d abscès"*

Cavitary Form of Cancer of the Lung —Cavitation with putrid content is observed in (1) chronic pneumonitides (2) acute pulmonary infections in diabetics (3) Friedlander's pneumonia (4) sarcoid disease of the lungs (5)
of the lung
is found in
in nature until proven otherwise

Cavitary cancer is found chiefly in the squamous cell type only about one fifth of the cases were observed in other cell types The cavity,

usually located in the center of the tumor results from closure of a bronchus from an inadequate blood supply to the new growth or sometimes it follows an intense course of radiation therapy The degenerated mass may remain *in loco* and be discovered at autopsy (Figs 60 and 61)



Fig 60 —Cancer of the upper lobe with cavity formation



Fig 61 —Cancer of the lower lobe with cavity formation

or crumble and be expectorated leaving an excavation which becomes infected and putrid, an excavation similar to chronic or acute abscesses of the lung with which it has been confused With the advent of putrefaction the crumbling of the tumor accelerates and often brings the necrotic matter close to the pleura which it erodes Its contents then pour into the pleural cavity producing an empyema Empyema in cancer of the lung is occasionally induced by a bronchopleural fistula The latter can readily be discovered by the intrapleural injection of a weak solution of methylene blue which in the presence of a fistula will appear in the expectorated sputum



Fig 62—Cancer of the right middle lobe with cavity formation Posteroanterior and lateral views

In about 70 per cent of cases reported in the literature the cavity was found in the upper lobes and in about 2 per cent in the middle lobe (Fig 62) Men were more frequently affected than women probably because squamous cell cancers which usually undergo the central necrosis are more commonly observed in men

While as a rule the clinical manifestations develop insidiously instances have been recorded where the onset was stormy accompanied by chills and fever as in acute lung abscess In the differential diagnosis the following points are significant

1 Aspiration abscess usually occurs postoperatively, particularly after oral surgery, such as tonsillectomy or tooth extraction

2 It also occurs in alcoholics who have been stuporous for a considerable length of time, and in consumers of large quantities of sedatives who have been in a deep and prolonged stupor

3 It can also be explained by a history of the penetration of a foreign body

Not more than 1 per cent of all lung abscesses are caused by aspiration of a foreign body, whereas about 10 per cent are found in lung cancer (Table 7)

Table 7. Cavitary Form of Cancer of the Lung

Authors	*Cancers*	*Cavities*	*Per cent*
Brock	477	83	17.50
Fishberg and Rubin	51	15	24.35
Hauser and Wolpaw	127	15	12.00
Jaffe	100	12	12.00
Koletsky	100	30	30.00
Maxwell	314	30	10.80
Rosedale and McKay	37	18	48.65
Strang and Simpson	1930	70	3.60
Total	3136	273	8.70

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Summary—In a case of lung abscess in a person of middle or past middle age, particularly in a male, the diagnosis of lung cancer should be given preference until proven otherwise

2

Pleural Effusion

A pleural effusion in cancer of the lung may appear in the early phases of the disease It results from an occlusion of the bronchus due to plugging with mucous which causes elevation in the intrapleural pressure, thus leading to a pleural effusion The exudate results from the obliteration or damage of the submesothelial pleural circulation It may

be produced by an intrathoracic as well as extrathoracic disease Pathogens, tubercle bacilli and neoplasms (malignant or benign) may be responsible for the accumulation of fluid in the pleural cavity It was observed in women with benign ovarian fibromas, so-called "Meigs's syndrome" It also was observed as a local manifestation of a systemic disease, such as lupus erythematosus, cirrhosis of the liver, and nephrosis

When found in a young adult or adolescent, it is presumably tuberculous until proven otherwise, but in persons of middle or past middle age it is more likely to be neoplastic or cardiac in origin (Fig 63)



Fig 63—Bronchiogenic cancer of the left lower lobe pleural effusion (arrows) due to pneumonitis Clearing of effusion after administration of antibiotics

In a study of 216 patients with primary tuberculous pleursy, Robertson found that 117, or 54 1 per cent, occurred under the age of 20, 60, or 27 8 per cent, between 20 and 29 19, or 8 8 per cent between 30 and 39 Between the ages of 40 and 49 only 20 cases, or 9 3 per cent, were due to *Mycobacterium tuberculosis* Leuallan and Carr found that of 229 patients with neoplastic diseases, 52 5 per cent showed pleural effusions Of these, 41 5 per cent occurred in cancer of the lung, 23 1 per cent in cancer of the breast, and 12 2 per cent in lymphomas and leukemias Sahn and his associates, in a study of 103 pleurisy patients whose ages ranged from 50 to 87, found that in 45 instances (43 7 per cent) the effusion was due to carcinoma, and in 36 instances (35 per cent) to congestive heart failure In only 1 instance was it due to tuberculosis

Pleural effusions were observed in mediastinal tumors and in cancer of the kidney, stomach, large bowel, and ovary

The notion that a hemorrhagic fluid is produced invariably by a malignant disease has been disproven Tuberculosis of the lungs and pleura, congestive heart failure, pulmonary infarct, and some systemic diseases, such as cirrhosis of the liver or nephrosis, have been observed to yield hemorrhagic pleurisies Metastatic tumors may produce serous as well as hemorrhagic effusions The highest figures of bloody pleural exudates, about 30 per cent, are found in metastatic mammary cancer

DIAGNOSIS

The diagnosis of a pleural effusion based on clinical findings alone is generally presumptive In order to ascertain the presence of fluid in the pleural cavity, a thoracentesis is a prerequisite Even though the malignant origin of the exudate found in a cancer patient usually proves a foregone conclusion, the disclosure of neoplastic cells in the fluid is just as important as the performance of a lymph-node biopsy in a person known to suffer from cancer The detection of malignant cells in the effusion presents no difficulties It is well to remove as much fluid as possible and to store it in the ice chest for several hours in order to allow the cellular elements to settle The supernatant fluid is then decanted, and the remaining fluid is centrifuged The supernatant fluid is again discarded, and the sediment is then used for the following tests

1 *Paraffin Block Sections* —The sediment is carefully withdrawn from the centrifuge tube and placed on a piece of filter paper about 1 inch square It is then fixed in a 5 per cent solution of formaldehyde or in Zenker's fluid and run through the usual series of solutions Following this, paraffin blocks are prepared, cut, and stained with the customary dyes However, instead of running the sediment through several solutions, which consumes a considerable length of time, the sediment (on filter paper) can be boiled for 2 or 3 minutes in a 5 per cent solution of formaldehyde Frozen sections are then cut and stained with hematoxylin and eosin (Fig 64)

2 *Papanicolaou Method* —Smears prepared from the sediment (as described above) are placed on glass slides Like those of the sputum or bronchial washings, these smears should be fixed at once in a solution of equal parts of ether and 95 per cent alcohol They should be either stained by the Papanicolaou technique or with the Giemsa stain

Results —In a study of a large series of cases, Chapman and Whalen obtained 94 per cent correct diagnosis They have stressed that, in order to arrive at a positive diagnosis, the presence of fully or partially formed acini or of sheets composed of cells showing definite evidence of anaplasia is required Tegaki stated "The only reliable and useful

criteria for malignancy (in paraffin sections) are (1) clusters of malignant cells with an organoid arrangement (2) individual cells with malignant characteristics (3) cells stained positively for mucin" In his experience the use of paraffin blocks yielded a higher percentage of correct diagnoses than smears prepared according to the cytological method of Papanicolaou Thus in sections prepared from the paraffin blocks correct diagnoses were obtained in 51 cases suspicious diagnoses



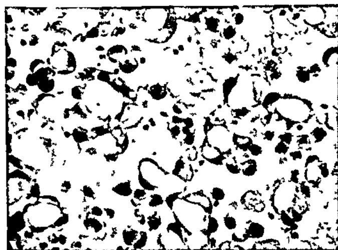


FIG 64 —Neoplastic cells in pleural effusion (paraffin sections)

pyridoxin to the solution A course of treatment consists in 4 to 6 injections administered at weekly intervals

For the intrapleural injection a dose of 4 mg per kg of body weight is used The injection of the nitrogen mustard solution is preceded by the withdrawal of most of the fluid from the pleural cavity The drug is infused through the thoracentesis needle which has been left in place

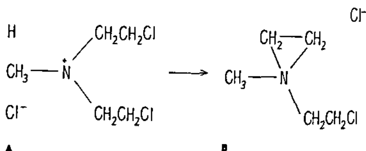


FIG 65—The chemical formula of nitrogen mustard *A* methyl bis (beta chlorethyl) amine hydrochloride (HN_2) *B* ethylenimmonium derivative of HN_2

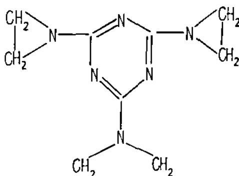


FIG 66—The chemical formula of TEM—triethylene melamine

The patient is instructed to change his position from time to time for 2 or 3 hours following the injection for the same reason as in the use of radioactive gold On the next day another thoracentesis is performed and as much fluid as possible is withdrawn

The state of the patient s homopoietic system should be investigated prior to the initiation of the therapy and for some time after its cessation Leukopenia is likewise one of the complications of this type of therapy Other complications such as nausea and vomiting are transitory and can be controlled without difficulty

The general condition of the patient is of importance Only patients whose general condition is good should be given a therapeutic trial

Although the effect produced by both remedies is quasi similar the

use of HN2 is preferable for the following reasons (1) it is much less expensive (2) it is easily obtainable (3) it can be administered by the attending physician at the patient s home (4) it carries no hazard to the personnel involved in administration of the treatment

TEM or triethylene melamine (Fig 66) is a substance which is chemically related to methyl bis (beta chlorethyl) amine that is to HN. Studies have revealed that the cytotoxic effect of the two substances on normal and neoplastic cells is about the same The advantage in the use of TEM consists in its lesser toxicity and particularly in its effectiveness when given orally

3

Osteoarticular Manifestations

Patients with primary cancer of the lungs often complain of crippling pains in their bones and joints In many patients the disease *starts* with this symptom which is so pronounced that it fully absorbs the attention of both the patient and the physician In many other patients the symptom makes its appearance in the presence of a small pulmonary cancer Indeed just as the painful shoulder in the case of the apical cancer was diagnosed as bursitis or neuritis while the tumor was overlooked so in these cases the osteoarticular manifestations were diagnosed as an infectious arthritis while the pulmonary tumor remained unnoticed—until the terminal stages

In 14 of 139 patients observed by Ray and Fisher the initial complaints referred to painful joints In 5 of the patients the arthralgia preceded the pulmonary symptoms by 5 months Hansen reported that of 100 patients studied by him 12 complained of joint pains In 4 of the patients it appeared as an initial manifestation of the disease In 17 of 22 patients with cancer of the lungs observed by Hammarsten and O Leary joint symptoms were the first manifestation of the malignant disease The articular pains preceded the chest symptoms by more than 18 months In 3 of 20 patients with neoplasms the chest x ray films were not considered suggestive of cancer Of 14 tumors in patients who had thoracotomies 9 were resectable Several of my patients had been treated for osteoarthritic symptoms prior to the identification of the pulmonary cancer In some of them the malignant disease was discovered about 1 year after the onset of the joint symptoms

It is of further interest that the patients ultimately showed generalized hypertrophic osteoarthropathy

Illustrative Cases

Case 4 History—In this man the illness *started* with pain in the ankle, knee, and shoulder joints, which had become hot, red and swollen, totally disabling him After a 3-month period of unsuccessful treatment at home, he was hospitalized successively in three institutions, where diathermy and salycilates afforded relief No disease was found in the lungs The improvement of the arthritic condition was of short duration, however, and he was admitted to another hospital Here examination showed the wrists, elbows, hands, knees, ankles, and feet to be swollen, hot and tender, and their motion restricted Within the next 2 months the articular pains became so intense as to require large doses of sedatives and analgesics At this juncture attention was drawn to a small hemoptysis, and when the lungs were reexamined a cancer was disclosed Simultaneously, a generalized hypertrophic osteoarthropathy was noticed (Fig 67)

Case 5 History—A man 55 years of age was admitted to the hospital complaining of pain and stiffness in the joints of his *hands and feet He had smoked 20 cigarettes a day for many years* and for long had been bothered by a cough that produced tenaceous sputum

The present illness began about 2 years prior to his hospitalization with pains in the joints, which steadily grew worse About 7 months before admission he became bedridden His cough increased in intensity, and on one occasion he brought up a small amount of blood He developed night sweats, had been losing weight and, on moving, suffered pain in all joints

An area of dullness was disclosed in the lower portion of the right lung, which, on roentgenological examination, suggested pneumonitis or, possibly, chronic abscess Hypertrophic osteoarthropathy was found in the long bones The patient improved after a few weeks of treatment and was discharged

At home he suffered a relapse The pain required large doses of sedatives and narcotics He developed convulsive seizures, which were interpreted as probably owing to a metastatic cerebral abscess He reentered the hospital, and 3 weeks later he died

The autopsy disclosed a cancer of the right lung that contained a huge cavity in the center No metastases were discovered in the viscera or the brain

Comment—In these patients the onset of the disease and the subsequent clinical course were dominated by severe osteoarthritic symptoms which entirely overshadowed the mild pulmonary manifestations

Case 6 History—A man 41 years of age was admitted to the Montefiore Hospital complaining of pains in the bones and joints

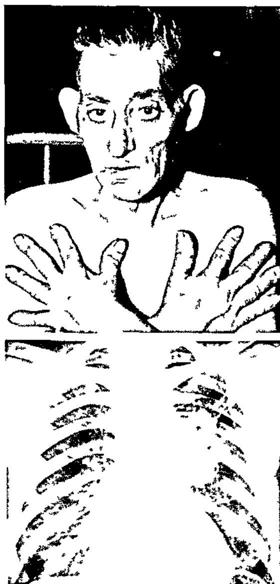


Fig 67 —Generalized hypertrophic osteoarthropathy Acromegalic appearance of patient with large hands and clubbed fingers X ray film shows a cancer of left hilus A biopsy revealed a squamous cell carcinoma

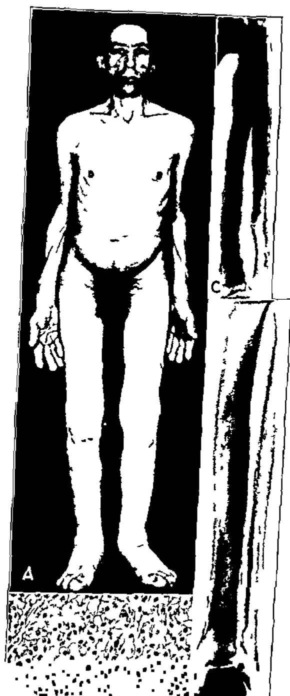


FIG 68 —*A* photograph of patient *B* histological structure of the cancer *C* Roentgen appearance of ulna and radius *D* tibia and fibula with extensive periosteal overgrowth

The illness *started* with painful swelling involving the ankles knees and joints of the upper extremities successively He was treated in three hospitals where the lungs were found to be normal The upper extremities showed limitation and pain in all joints on motion The wrists and elbows were swollen and warm The hands were also considerably swollen as were the proximal interphalangeal joints The knees ankles and feet too were hot and tender which made motion limited and painful The feet were greatly enlarged There was a considerable gynecomastia

Bronchoscopic examination failed to reveal abnormalities but an aspiration biopsy of the lung revealed tumor tissue that suggested a metastasis

The patient was discharged from the hospital after 2½ months but was readmitted 2 weeks later In the interval he had gained 4 pounds in weight but a productive cough small hemoptyses and dull pain in the right hemithorax had developed and the pain in the knee joints had become aggravated The pain in the joints was so severe that large doses of sedatives were required His temperature averaged *100 to 101° F*

In the right lung there was an area of dullness bronchovesicular breathing decreased vocal fremitus and moist rales were found anteriorly between the fourth and the sixth ribs On roentgenological examination the shadow previously seen in the right lung was now enlarged He was discharged and shortly afterward entered the Montefiore Hospital

At Montefiore the following observations were recorded (*1*) there was evidence of considerable loss of weight (*2*) the joints of the hands shoulders feet and knees were considerably swollen and painful (*3*) the lower limbs were massive clumsy and shapeless (*4*) the hands resembled spades or paddles (*5*) the fingers showed pronounced clubbing (*6*) the joints of the knees and ankles contained small amounts of fluid (*7*) there was a general adenopathy and gynecomastia (*8*) the lower two thirds of the right lung was dull to percussion and the breath sounds in this area were not audible (*9*) the patient's features were coarse and the

thickening and irregularity of the periosteum along the shafts of the humeri ulnae radii tibiae and fibulae (Fig 63) In the pelvis there were hypertrophic changes along both ilia and femurs The sella turcica was large but there was no evidence of destruction

Bronchoscopic Examination—This revealed a large friable mass completely occluding the bronchus of the right lower lobe of the lung below the apical branch The patient died after 5 months in the hospital

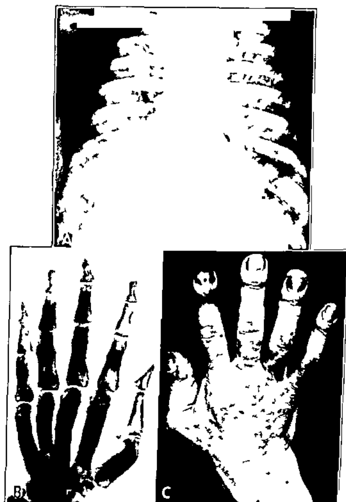


Fig 69 —*A* carcinoma of the lower lobe of the right lung *B* Roentgen appearance of the left hand showing lamellar periostitis *C* photograph of the right hand with clubbed fingers

Diagnosis —Bronchiogenic carcinoma right generalized hypertrophic osteoarthropathy, endocrinopathy

Autopsy —The right lung was adherent to the wall of the chest and the diaphragm The lower lobe was voluminous and firm It contained a tumor that measured 8 cm in diameter and extended from the hilus toward the middle of the lung The adrenals contained several cortical adenomas and the anterior lobe of the pituitary was prominent

Microscopically the tumor was a squamous cell cancer The pituitary showed hypertrophy and hyperplasia of the eosinophilic cells of the anterior lobe

Comment—Cases 4 5 and 6 illustrate cancers of the lung in which the *first* manifestations referred to arthralgias for which the patients were treated while the malignant disease remained unnoticed In some cases the cancer was in the inceptive stage and could not been seen with the x rays

GENERALIZED HYPERTROPHIC OSTEOARTHROPATHY

Bones Affected—Generalized hypertrophic osteoarthropathy is a condition in which the bones the joints and the soft tissue of the upper and lower extremities are affected Not all bones are involved with equal intensity and even in the same bone the lesion is more pronounced in the diaphysis than in the epiphysis The tibia and humerus are usually more frequently affected than other bones and in some cases the clavicles ribs scapulae and vertebrae are involved

Acromegaly and Pulmonary Osteoarthropathy—The patients resemble those with acromegaly with whom they had been confused until Pierre Marie dissociated the two diseases Their features are coarse their foreheads furrowed their lips thick and their mandibles prognathic Their hands are voluminous long massive and spade like The fingers resemble sausages and the distal phalanges show fusiform swelling or clubbing Their feet too are large and doughy with club shaped toes The terminal phalanges show tufting as in acromegaly Indeed many other characteristics of people with acromegaly such as hirsutism gynecomastia bulldog skull and splanchnomegaly are also found in these patients (Fig 70)

Pathological Anatomy—The disease starts in the periosteum as a productive periostitis (osteophytosis) but the possibility that the bones are primarily involved cannot be excluded The new periost is formed layer by layer the new layer superimposed on the preexisting one (onionskin layers) giving the newly formed periost a lamellary appearance (Fig 71) As in other diseases of the skeleton the bones and the periosteum are synchronously affected there occurs a new formation of bone (hyperostosis) causing an increase in the size and thickness of the bone and a rarefaction *i e* osteoporosis The corticalis and the compacta are thinned out The process may be defined as a hypertrophic porotic osteoporosis

The digits assume a club or drumstick shape due to edema and to a proliferation of the soft tissue around the terminal phalanges The nails become thickened and curved resembling the beak of a parrot and the nail beds grow red and cyanotic particularly in the active stages of the process

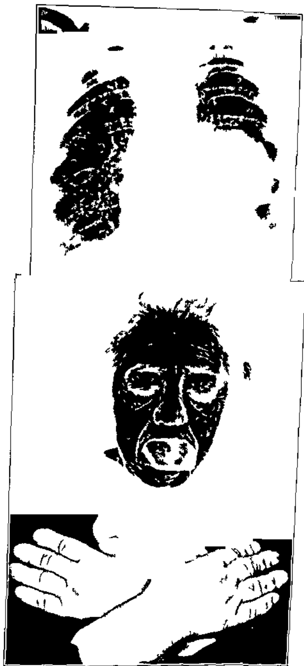


Fig 70—Photograph of patient with redundant eyelids macroglossia swollen hands clubbed fingers and hirsutism Roentgen appearance of cancer of lower lobe of left lung



Fig 71 —Bronchiogenic cancer of the left apex Roentgenogram of the right hand and left foot showing extensive wart like periosteal overgrowth and tufting of the terminal phalanges In the inset is the patient s acromegalic (oval) face showing prognathism and left Horner s syndrome

The shape of the nail is, indeed, the deformity to which Hippocrates originally called attention Pigeaux, in 1832, was the first to use the term "Hippocratic fingers," though unaware of their link with generalized osteoarthropathy, which was not understood at the time At present, it is universally accepted that clubbed fingers are a part of the disease

In the soft tissues surrounding the affected bones there occur proliferative and indurative changes leading to a thickening of the skin and the subcutaneous tissue The skin assumes a "doughy" aspect, giving the false impression of edema

Bones in Syphilis and Paget's Disease.—In hypertrophic osteoarthropathy as with acromegaly, the bones show an increase in thickness but not in length In syphilis and Paget's disease, originally confused with

where it proliferates prodigiously The teeming spirochetes irritate the cartilagenous cells, accelerating their transformation into osseous cells *and simultaneously enhancing their proliferative activity This, in turn,* leads to a cellular overproduction, resulting in elongation of the bone (The process occurs in individuals of growing age, before 20 years of age)

It is of interest that, unlike the tibia, *the fibula is only scantily invaded* by spirochetes, and as a result, the growth of the bone proceeds along quasi physiological lines Since the two bones are firmly attached at the ends, the faster growing tibia will of necessity bow, while the fibula

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has ceased, the elongation is due to a complete rebuilding of the bone proper, with an excessive formation in length, width, and thickness The old bone is destroyed by osteoclasts, and the fat marrow is converted into fibrous tissue, while the newly formed bone, built for the greatest part by osteoblasts, persists as osteoid

It is thus evident that the skeletal changes in generalized hypertrophic osteoarthropathy differ from those observed in syphilis and in Paget's disease They are, however, a replica of the skeletal changes seen in acromegalic bones It is believed that the two processes are related etiologically

PATHOGENESIS

Circulatory Disturbance—In 1832, Pigeaux wrote, 'The formation of curved nails is influenced by embarrassment in circulation generally it occurs in all conditions affecting 'hematosis'" Pigeaux had no knowledge of generalized hypertrophic osteoarthropathy, and like his predecessors

and successors to the day of Pierre Marie (1853–1940) he was concerned solely with the clubbed fingers and the curved nails which he found in tuberculous and "marantic" individuals Of 200 phthisic patients studied by him 67 showed "*griffes hippocratiques*" (Hipprocratic claws) One third of these were marantics He stressed "The curvature of the nails and particularly the development of the fusiform shape of the fingers is of extreme importance as a prodromal sign in latent tuberculosis and still more in the derangement of 'hematosis' " He observed that this development may grow or diminish in severity and even disappear and that it occurs more frequently in women than in men

Tuberculosis —The eminent physician Trousseau* stressed that tuberculosis is the cause of clubbed fingers The Hipprocratic fingers" he wrote "are characteristic of tuberculosis only Not all tuberculous individuals have Hipprocratic fingers but those who have them are with few exceptions tuberculous He went on when patients with a chronic catarrh accompanied by bronchial dilation reveal signs of phthisis I am opposed to the diagnosis of tuberculosis if Hippocratic fingers are lacking

The dogmas of tuberculosis (Pigeaux Trousseau) or of pulmonary suppuration (Pierre Marie) as etiological factors have been abandoned but the concept of hematosis is still in vogue Attempts to reproduce some kind of "hematosis by experimental means have yielded either negative or ambiguous results Moreover as is well known general hypertrophic osteoarthropathy appears in the absence of signs of impaired circulation or oxygenation and long before a tumor of the lung has attained a size that could possibly affect the respiration or the circulation

Dyspituitarism —The concept that generalized hypertrophic osteoarthropathy is in all likelihood caused by an endocrine disturbance dyspituitarism is based on the following premises †

*Armand Trousseau (1801 1867) one of the most prominant European clinicians author of a multivolumed treatise *Traite de therapeutique* which has been translated into the English language and published in many editions The quotation

ung—wh h he co ld not identify And what did he mean by the term Hipprocratic fin

a rudimentary knowledge of cancer in general and cancer of the lung in particular Autopsies were rarely performed by competent pathologists Cancer and tuberculosis were usually confused

†See Fred B M Chronic pulmonary osteoarthropathy—dyspituitarism as a probable cause Arch Int Med 72 565 1943

by unknown processes From a review of a large series of reported cases, the authors deduced that aneurysm of the aorta was responsible for the syndrome in 69 per cent of cases, malignant tumors were responsible in 35 9 per cent, and syphilis (syphilitic mediastinitis and aortic aneurysm) was the cause in 34 8 per cent of cases

In a study of 38 cases with superior vena cava obstruction due to cancer of the lung, it was found that in 30 instances the tumor arose in the right lung, and that in 90 per cent of cases it was made up of undifferentiated cells

Diagnosis —The diagnosis is usually made by comparing the measurements of the venous pressure in the upper and lower extremities In fact, this may be the only practical method for recognizing the obstruction The venous pressure in the arms is significantly higher than in the femoral venous pressure The arm to-tongue circulation time may be normal in spite of the fact that the venous pressure is quite high If prolonged it is usually less than might be anticipated from the height of the venous pressure

Venous angiocardiography is the method chosen for diagnosis of the obstruction that will give topical information when treatment is under consideration Jacobs and his associates have utilized the saphenous vein instead of the antecubital vein for the injection of iodopyracet into the blood stream In their experience, this route has given more satisfactory results

Treatment.—The treatment depends on the etiology of the obstruction, whether it be tuberculous, syphilitic, inflammatory or neoplastic In non neoplastic diseases, decompression procedures (medianostomy) are used They afford symptomatic relief and provide time for the development of a collateral circulation In cancer of the lung, radiation and mustard gas therapy are used with palliation in a large percentage of cases

Except for cancer, the prognosis is not necessarily unfavorable Zeman reported a case of a man 68 years of age who was under his observation for 19 years The cause of the obstructive signs and symptoms in the patient had been explained on the basis of a syphilitic mediastinitis with secondary venous thrombosis Hansen and his associates reported a new operative procedure successfully used by them on a girl 9 years of age whereby the azygos vein was anastomosed to the right atrium In their case the possibility of a congenital deformity of the superior vena cava causing the syndrome could not be excluded McArt and his associates observed the superior vena cava syndrome caused by an intrathoracic goiter The patient was cured after a subtotal thyroidectomy They suggest that substernal goiter should be considered in the differential diagnosis of the syndrome

5

Recurrent Peripheral Thrombophlebitis

of the abdomen It tends to regress and recur Unlike infectious or marantic thromboses the thrombosed vein in cancer patients show virtually no sign of inflammation

Trousseau was probably the first to call attention to this phenomenon He wrote "When you are uncertain about the nature of a disease of the stomach whether it is a chronic gastritis an ulcer or a carcinoma the finding of *phlegmasia alba dolens* in the leg or arm will dispel your doubts and enable you to state that you are dealing with a carcinoma I have demonstrated cases of obliterative phlebitis in carcinoma of the stomach as well as in cancer of other organs"

Sproul in an analysis of 4 258 autopsies on cancer patients found multiple thrombosis in 31 1 per cent of cases of carcinoma of the tail of the pancreas in 1 3 per cent of carcinoma of the stomach and in 2 5 per cent of carcinoma of the lungs In Edwards 29 cases of thrombophlebitis—23 from literature and 6 of his own—16 were found in carcinoma of the pancreas 4 in carcinoma of the stomach 2 in carcinoma of the gallbladder 4 in carcinoma of the lungs and 3 were of unknown origin Barker in an analysis of 166 cases of peripheral thrombophlebitis found carcinoma to be the most frequently associated condition (at times in fact the *first* clinical manifestation) particularly in carcinoma of the lung and the pancreas Cooper and Barker reported 4 cases with recurrent venous thrombosis in cancer of the lung—undiagnosed until autopsy The pulmonary signs and symptoms as well as the *x* ray appearance had been interpreted as a pulmonary infarct

Fisher and his associates reported 4 cases in which thrombophlebitis antedated the onset of manifestations of primary pulmonary cancers by several months

It is the consensus that the occurrence of a recurrent migratory thrombophlebitis which cannot be attributed to any of the known causes (such as operations pregnancy blood dyscrasias thromboangitis obliterans or prolonged bed rest) points toward the possibility of an obscure visceral cancer

The etiology of the spontaneously occurring phlebitis in visceral cancer is not understood It occurs in patients with no sign of debility or dehydration and in the absence of local pressure or stasis The composition of the blood too—its dynamics as well as its coagulability—has provided no clues

6

The Brachial Plexus Syndrome

The Brachial Plexus—The brachial plexus is made up of the anterior primary division of the fourth fifth sixth seventh and eighth lower cervical nerves and of the greater part of the thoracic nerve After emergence from their respective intervertebral foramina the nerves converge toward the upper border of the first rib unite to form three trunks

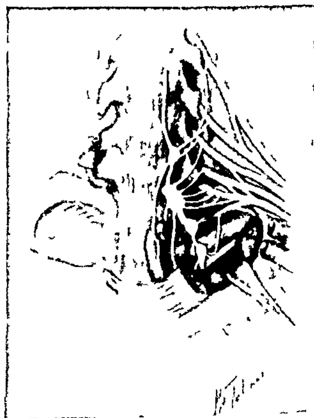


Fig 74—Diagram of an anatomical preparation showing region invaded by a tumor of the left thoracic apex The clavicle and sections of the subclavian artery and vein have been removed The apex of the lung together with parietal pleura ... xth
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and then divide into cords from which the nerves of the upper extremity are derived (Fig 74)

The Syndrome—This syndrome is made up of several components Pain in the shoulder girdle is one of the earliest and most outstanding The pain is persistent and often so severe as to absorb fully the attention of the patient and physician alike In fact the pain is the chief complaint throughout the entire course of the illness Therapy is usually

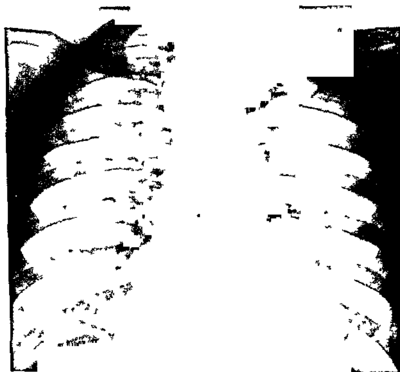


Fig 75—Cancer of the left pulmonary apex (superior pulmonary sulcus tumor)

concentrated on the painful shoulder joint—diagnosed as bursitis or arthritis—while the apical cancer which is primarily responsible for the symptoms is overlooked until incidentally discovered by the roentgenologist or until the appearance of a superficial (supraclavicular or infraclavicular) adenopathy

The brachial plexus syndrome is also of interest because it demonstrates the aberrant manifestations so often observed in cancer of the lung as in many cancers of other organs Formerly clinicians when faced with

"erratic" symptoms, always suspected *syphilis* as the cause (*"cherchez la syphilis"*) Physicians of our era should apply this dictum to cancer (*"cherchez le cancer"*)

The brachial-plexus syndrome (often called the "Pancoast syndrome) is due, not so much to the *malignant disease per se*, as to its topography The tumor encroaches on the brachial plexus, producing at the onset a reactive neuritis and, ultimately, a full fledged syndrome The components of the syndrome will be taken up one by one

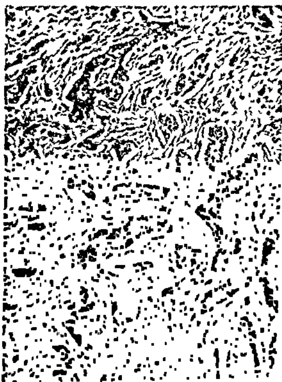


Fig 76—The apical cancer embedded in scar tissue Such cancers have been erroneously described as having originated in a scar (*Narbenkrebs* or scar cancer)

Topography of the Tumor—The cancer arises in the mucosa of the terminal bronchiole at the very apex of the lung With the roentgen ray films it is seen as a convex density beneath the dome of the pleura, casting a shadow characteristic of a thickened pleura or of a fibrotic tuberculous scar (Fig 75) The tumor is usually embedded in dense fibrous tissue having the structure of a healed tuberculosis (Fig 76)

where it reaches the brachial plexus induces a reactive neuritis at first and ultimately through pressure and infiltration a constant neuritis

Pain—The early symptoms refer to pain in one or several points the shoulder the scapula the anterior upper part of the thorax the axilla the ulnar side of the forearm and the inside of the arm The pain which is usually restricted to a limited area is sharp burning or shooting and shows remissions It is related to the involved spinal nerves to the irritation of the upper thoracic nerves as they emerge from the intervertebral foramina or to an encroachment of the tumor on the parietal pleura which is provided with fibers from the intercostal nerves (Fig 77) Stimuli arising in the parietal pleura produce surface pains that have a segmental distribution

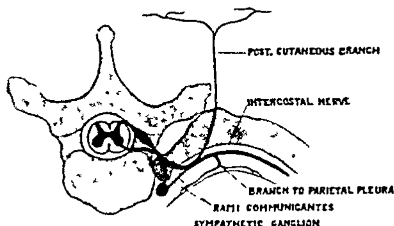


Fig 77—Diagram showing the components of the thoracic spinal nerve (Ray B S Tumors of the apex of the chest courtesy of Surg Gynec & Obst 67 577 1938)

All nerves of the brachial plexus may be simultaneously involved When the cervical plexus is affected pain occurs in the side of the neck radiating to the jaw or behind the ear When the trunks are involved the symptoms are radicular but when the cords are involved the pain is referred to the peripheral nerves

Muscular Atrophy—Pain is accompanied by weakness and by atrophy of the arm of the affected hemithorax The atrophic changes begin in the smaller muscles of the hand (the hypothenar and interossei) because of the early involvement of the lower nerves (the eighth cervical and the first thoracic) of the brachial plexus

Paresthesias—Paresthesias as evidenced by a sensation of tingling and pins and needles are of frequent occurrence

Paralysis—Two types of paralyses are distinguishable

1 The Duchenne Erb or upper arm type in which the fifth and sixth cervical roots are involved the roots and trunks between the first ribs or clavicle and the transverse processes of the vertebra being compressed

2 The Dejerine Klumpke or lower arm type of paralysis results from the involvement of the nerves derived from the eighth cervical and first thoracic roots (Fig 78)



Fig 78—A patient with cancer of the left pulmonary apex There is swelling of the left supraclavicular fossa a homolateral Horner's syndrome left monoplegia and edema of the left arm

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the vasomotor and sudomotor activities of the facial skin (Figs 55 and 78) It results from the destruction of the thoracocervical ganglionic chain at or above the first thoracic sympathetic ganglion In some patients anhydrosis of the face probably precedes the ocular changes This is to be expected because the apical cancer first encroaches upon the nerves below the first thoracic sympathetic ganglions causing a sympathetic and not an ocular paralysis

Lindgren reported a case in which the skin of the affected side was less pigmented following ultraviolet irradiation than that of the non affected side The zone of pigmentation was sharply demarcated by the mid line and although the face and neck subsequently became pigmented the difference in pigmentation on the chest and back remained until

the patient's death The failure of the skin to show pigmentation was attributed to an involvement of the sympathetic nerves by the apical tumor

Miscellaneous Symptoms —*Respiratory* —Cough expectoration, hemoptysis and blood streaked sputum as well as systemic disturbances appear in the later stages of the disease but are usually eclipsed by the neurological manifestations

Metastatic —As in cancer located in other parts of the lung the apical cancer metastasizes to distant organs including the adrenals and the brain Skeletal metastases are detected first in the upper three ribs on the ipsilateral side and in the clavicle

Diagnosis —Pain in the shoulder girdle which is frequently the earliest manifestation is usually attributed to "rheumatism arthritis" or bursitis and the dense area seen with the x rays is misinterpreted as a thickened pleura or a fibrotic tuberculosis The diagnosis is usually arrived at when the disease is advanced and no longer amenable to effective treatment

The apical location of the tumor precludes a bronchoscopic inspection Whether bronchial washings are apt to yield cancer cells remains to be ascertained The following procedures should be resorted to whenever possible (1) a scalene node biopsy should be performed even though the node may not be palpable or may appear manifestly normal (2) a puncture biopsy

Differential Diagnosis —As stated above the tumor is mistaken for tuberculosis or for a degenerative lesion of the shoulder joint It has also been mistaken for the scalenus anticus syndrome

Scalenus Anticus Syndrome The scalenus anticus muscle is attached to the anterior tubercles of the transverse processes of the third fourth fifth and sixth cervical vertebrae from where it courses downward and is inserted in the scalene tubercle on the inside of the upper surface of the first rib It is located in front of the subclavian artery and brachial plexus and behind the subclavian vein The components of the brachial plexus which emerge from their respective foramina lie behind the medial surface of the muscle

The symptoms (motor and sensory) are caused by irritation or compression of the brachial plexus which is initiated by spasm or hypertrophy of the scalenus anticus muscle The Horner's syndrome does not follow the scalenus anticus syndrome unless the brachial plexus has been injected with procain for therapeutic purposes

Branchiogenic cancer is clinically a counterpart of the cancer described above It has been found to originate *above* the dome of the pleura and from the lower *branchial* cleft Like the apical pulmonary cancer the branchiogenic cancer induces the characteristic brachial plexus syndrome

Neurogenic and *thymogenic* tumors have been found to induce the same syndrome

Metastatic tumors from various abdominal viscera and also from the breast and cervix occasionally reach the pulmonary apex and induce manifestations quasi similar to the primary apical lung cancer It is necessary to be on guard against such an eventuality

Treatment —Palliation has been obtained by the use of nitrogen mustard and radiation Therapy had been applied too often when the disease was advanced Chardack and MacCallum dared to approach the problem surgically They operated upon a 54 year old male patient with a cancer in the right pulmonary inlet that had produced a brachial plexus syndrome The tumor extended through the apex of the pleural dome into the brachial plexus involving roots T–1 and C–7 Surgical removal was accomplished and followed by radiation therapy No recurrence of the neoplasm was noticed for 5 years after the operation The patient remained asymptomatic

Untreated patients rapidly deteriorate as a result of the narcotics which they consume in large quantities and which offers them slight relief The duration of the illness is about the same as in other types of pulmonary cancer extending from 1 to 1½ years from the time the diagnosis has been made

7

Neuropathy

It has been observed that neuromuscular disorders occur in patients with cancer of the lung with no metastases to the central nervous system and no involvement of individual nerves (by perineural infiltration) *with cancer cells The disorders have been classified as* (1) cerebellar degeneration (2) peripheral neuropathy (predominantly motor predominantly sensory or mixed) and found in about 2 per cent of cases

with carcinoma of the breast ovaries and stomach while neurop

have been observed in cancer of the lung only

British observers who have called attention to these disorders suggest the possibility of two dissimilar syndromes namely a cerebellar syndrome associated perhaps with cancer in general and a neuropathy associated with cancer of the lungs only No explanation for the neuropathy has yet been found It has been noticed however that in the majority of these cases the nervous disorder was the *first* evidence of the disease of the lung

8

Peripheral Lymphoadenopathy

In malignant epithelial tumors and in lymphomatoid disease the finding of a peripheral lymphoadenopathy is of diagnostic therapeutic and prognostic significance It is indeed imperative that every patient be thoroughly examined for the presence of superficial lymph nodes which may harbor a metastasis from a silent visceral cancer or a lymphoma

In the past the search for a peripheral lymphoadenopathy in cancer of the lung was largely neglected and the incidence was greatly underestimated With the advent of the modern therapeutic approach to pulmonary cancer such a search has become obligatory In a number of cases the cancerized lymph node may be the first and only evidence of a dormant malignant disease somewhere in the body in a number of other cases it will attest to the dissemination of the disease which therefore precludes the use of "heroic therapeutic measures While a minute bronchiogenic cancer will occasionally show a metastasis to a peripheral lymph node the peripheral nodes are most frequently invaded in the more advanced stages of the disease In cancer of the lung it has been found in from 20 to 25 per cent of cases

9

Cancer of the Lung and Tuberculosis

Cancer of the lung was regarded as a very rare disease (a museum specimen) in the nineteenth century while tuberculosis of the lung (the white plague) was quasi epidemic In the twentieth century however the picture changed when pulmonary cancer began to assume quasi epidemic proportions while pulmonary tuberculosis began to show a dramatic decline It was conjectured that the two processes were linked *i e* that a considerable percentage of salvaged consumptives (as well as those who did not contract tuberculosis) had survived only to attain the cancer age and become victims of pulmonary cancer It was further surmised that with the advent of modern antituberculosis therapy the number of salvaged persons would multiply and provide still more "candidates" for the malignant disease of the bronchus

The statements made by some observers that an etiological relationship exists between tuberculosis of the lung and cancer of the lung, and

by other observers that the two diseases are mutually antagonistic, are no longer considered valid Cases of the association (symbiosis) of tuberculosis and cancer in the same person, and also in the same lung, have been reported since the 1880s and for the past three decades many accounts of such cases have been published The problem has assumed particular importance because, according to epidemiologists, "tuberculosis has now become a disease of middle age and older persons predominantly" (Krupka and Breslow) They have estimated that the average age of death from pulmonary tuberculosis has increased from 33 3 years in 1929 to 49 9 years in 1950, an age at which cancer of the lung is encountered frequently



Fig 79—A tuberculous cavity with its wall covered by cancer cells

In some cases cancer cells were found covering the wall of a tuberculous cavity (Fig 79), and in others the cavity was filled with neoplastic tissue (Fig 80) In both instances the malignant diseases had been stated to have arisen in the wall of the cavity However, here as in nontuberculous patients, cancer arose in the wall of the bronchus, from where it penetrated the cavity The mechanism of cancerization of a tuberculous cavity in bronchogenic carcinoma is similar to the epithelialization of a bronchiectatic, tuberculous or an osteomyelitic cavity The notion that the epithelium "imported" into the cavity from the outside became cancerous is, to my knowledge, against the basic concepts of oncology Cancer found in tuberculous scars at the apices of the lungs

likewise did not originate *in situ*, but was imported from the adjacent bronchiogenic cancer

Clinical Contingencies.—From the clinical point of view the following possibilities are to be considered



Fig 80—A tuberculous cavity filled with cancer from the bronchus

1 *Cancer is being mistaken for tuberculosis*

2 *Tuberculosis is being mistaken for cancer*

3 Cancer and tuberculosis are associated (*a*) in the same lung, (*b*) in different lungs (Figs 81 and 82)

It had been a universal practice in former years to make an erroneous diagnosis of tuberculosis when cancer was present The opinion of Trousseau, as quoted on page 123, is a case in point Even in the first

decades of this century, patients with cancer of the lung were almost always diagnosed as tuberculous and referred to tuberculosis sanatoria (It was in such an institution that I had the opportunity to observe my first patients with cancer of the lung.) In fact, in the past almost *all* patients with pulmonary cancer were customarily referred to sanatoria

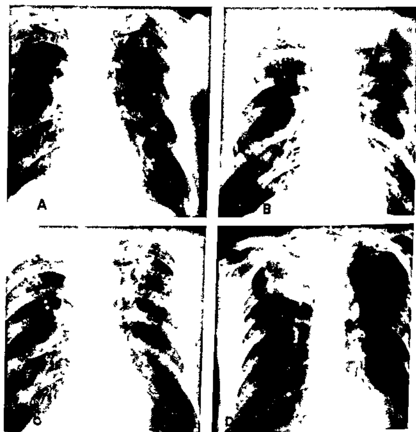


FIG. 81 —Carcinoma of the right upper lobe and tuberculosis of both upper lobes The 4 roentgenograms were taken over a period of 7 years *B* was taken 4 years after *A* *C* was taken 1 year after *B*, and *D* was taken 2 years after *C*

as tuberculosis cases Now, with the prevailing interest in pulmonary cancer, the reverse is taking place, *i e*, tuberculosis is being mistaken for cancer

When tuberculosis is complicated by bronchial stenosis, it is particularly apt to be confused with cancer Tuberculosis of the larger bronchi, virtually unknown three decades ago, is now found in about 30 per cent of individuals with pulmonary tuberculosis It usually leads to the forma-

tion of a scar with retraction and partial (occasionally complete) obstruction of the bronchial lumen inducing bronchial lesions that imitate a stenosis produced by cancer of the bronchus

Tuberculous proliferation that takes place in anthracotic tracheobronchial lymph nodes leads to a deforming bronchitis and gradually to an *occlusion of the lobar bronchus* *As in malignant bronchostenosis* atelectasis and atelectatic pneumonitis develop in the pulmonary lobe



Fig 82—Cancer of the lung originating in the right hilus and tuberculosis of both lungs Hydropneumothorax

and lead to permanent induration Pneumonectomies have been performed on patients with indurative pneumonitis which often induces *suppurative bronchitis i e pneumonitis abscess and gangrene (similar* to the abscess and gangrene observed in bronchiogenic cancer) Cough productive of blood streaked sputum and occasionally hemoptysis occur in the early stages of the disease Unilateral fibrocaseous tuberculosis is particularly prone to be mistaken for cancer

Bronchiogenic Cancer Combined with Tuberculosis of the Lung— Statistics hitherto reported estimated *a combination of the two diseases* to exist in about 15 per cent of cases of cancer of the lung. Generally figures depend on the interest of the particular institution in cancer, *tuberculosis, or both, and on the zeal of the pathologist.*

It was the contention of former authorities that the tuberculous lesion of these patients is usually of the healing or healed type, and that their sputums are invariably negative for tubercle bacilli. In my own investigations fibrotic, fibrocavitary and pneumonic types were found. The sputum was positive in more than one third of the patients, negative in one half, and not investigated in those remaining. With modern bacteriological methods of investigation, the percentage of positive sputums has been shown to be steadily increasing.

As a rule, the malignant disease developed in the older consumptives, two thirds of the patients were 50 to 70 years of age.

The patients may be divided into those whose *tuberculosis was asymptomatic* at the time when the cancer appeared, and those who had had symptoms of tuberculosis when the cancer appeared. In some of them the *malignant disease started abruptly with a severe "cold," "influenza," or* pneumonia," in others it developed insidiously with a steady loss of weight, increasing weakness and exacerbation of cough. In a few *instances the malignant disease revealed itself by a small hemoptysis or* blood streaked sputum.

The combination of the two diseases is encountered in one of two ways.

1. Cancer develops in the lobe affected by tuberculosis (Figs 81 and 82). In these cases tuberculosis, the easier disease to diagnose, takes the ascendency. The prompt improvement in the tuberculous patient—due to the use of the "magic drug"—and the disappearance of the pathogenic infection of the lung both eclipse the coexistent malignant disease.

2. Cancer develops in a lobe not affected by the acid fast infection. This is usually interpreted as a "spread" of the tuberculous infection.

In my own cases, as in those of others, the disease was originally diagnosed as tuberculosis, while the cancer was overlooked. In fact, most of the reports on the combination of the two diseases, published in the last few years, have originated in tuberculosis sanatoria.

The duration of the illness in the "symbiotic" group was, as a rule, not much shorter than in patients with carcinoma alone. The patients succumbed to cancer, not tuberculosis.

An early identification of the combination of tuberculosis and cancer is of primary importance from a therapeutic point of view, whether surgical or radiologic. The detrimental effect of *x* rays on a tuberculous process is widely known.

Tuberculoma—Not only is the fibrocaseous type of tuberculosis confused with cancer, but certain types of isolated tuberculous foci are also





Fig. 83.—Tuberculoma of the left upper lobe. Lobectomy. Lesion consists of a caseated center surrounded by a thick wall made up of tuberculous granulation tissue.

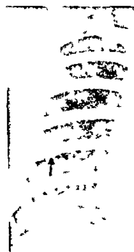




Fig. 84.—Tuberculoma, posteroanterior and lateral views. Incidental finding. Lobectomy.

liable to be erroneously interpreted as bronchiogenic cancer. Of particular interest is the so called tuberculoma which although identified in the brain long ago has only recently been recognized in the lung. On x ray examination it is visible as a round or ovoid dense shadow (usually single) which is well demarcated from the surrounding normal pulmonary

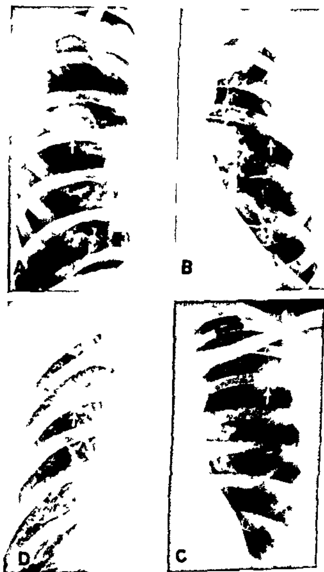


Fig 85—*A* tuberculoma in a patient with sputum positive for tubercle bacilli *B* bronchogenic cancer discovered at routine *x* ray examination *C* metastases from cancer of the breast *D* inoperable cancer of the lung

parenchyma (Figs 83 84 and 85) It often contains foci of calcium deposits which on cut surface may have a laminated appearance This finding is of importance because cancer very rarely shows calcified deposits The tuberculoma is usually located in the lower lobe and probably always in the vicinity of the pleura

The mass is as hard as stone due to calcification or hyalinization or it is somewhat pasty due to its caseous center (Fig 83) In these cases the lesion is enveloped in a thick fibrous capsule which on histological examination reveals tuberculous granulation tissue The size of the tuberculoma is variable ranging between 2 and 10 cm in diameter

Such a lesion is in all likelihood tuberculous although this finding has not been accepted universally Not only the histological structure of the capsule but its location as well speaks for its tuberculous nature probably a remnant of the primary infection with tubercle bacillus defined as the Primary Complex

The tuberculous nature of the lesion is disputed by some observers because of their failure to detect tubercle bacilli therein However Black and Ackerman found Koch s bacilli in 3 out of 15 cases Wang found acid fast microorganisms in 3 of 19 cases and Bleyer and Marks found the bacilli in 3 of 8 cases examined by them In many cases parenchymal tuberculous lesions were found in the presence of tuberculoma In fact whenever the tuberculous granuloma is discovered a search for tuberculosis in other parts of the lung should be instituted

To be sure a fungal infection or an infection with pathogenic microorganisms may induce lesions not unlike the tuberculoma The diagnosis is therefore beset with some difficulties Most of the patients are symptom free 72 per cent according to Wang and 50 per cent according to Bleyer and Marks In Black and Ackerman s series of 18 cases 6 were "silent" while in 12 the complaints were indicative of pneumonitis The percentage of cases diagnosed hitherto has been rather small Instances however have been observed in which the silent tuberculoma became active and induced a spread of the tuberculous infection It is the consensus of opinion that the lesion should be removed surgically

10

Cancer of the Lung in the Asthmatic

The danger of overlooking the advent of cancer of the lung in a person with a long standing cough is greater than in a person with no previous respiratory disease This holds particularly true of asthmatics in which the disease has a tendency to display periodic exacerbations

However if an asthmatic of middle age particularly a male begins to show intensification of his long standing ailment develops pain in the chest and constitutional changes the possibility of a malignant disease of the lung should be considered Generally the appearance of fever and of chills in asthmatics as in nonasthmatics warrants prompt investigation for bronchial obstruction *i e* bronchoscopy and cytobacteriological examination of the sputum It has been repeatedly observed that patients with bronchogenic cancer were treated as chronic asthmatics while the cancer itself went unnoticed

11

Cancer of the Lung and Bronchiectasis

Unilateral basal bronchiectasis complicated by pneumonitis yields physical and roentgenological signs not unlike those of cancer of the lung Episodes of fever blood streaked sputum and constitutional symptoms are suggestive of chronic bronchiectasis as well as of malignant disease of the lung A painstaking history and a thorough investigation are essential in order to arrive at a correct diagnosis

Bronchiectasis is encountered far more often in adenoma of the lung than in carcinoma of the lung This is due to the usual tightness of the bronchial occlusion in bronchial adenoma and to the protracted course of the disease In carcinoma of the bronchus a complete closure of the bronchial lumen is not always effected the tumor often crumbles making a "fenestration in the occluded bronchus and letting the air seep in Moreover the duration of the illness in carcinoma is not long enough to allow extensive bronchiectasis to take place In fact whenever a considerable amount of bronchiectasis is found in a patient with a lung cancer it has most likely preceded the inception of the cancer

12

Pneumonoconiosis Mistaken for Cancer of the Lung

Diseases of the lungs caused by dust may produce symptoms that suggest cancer of the lung Of particular interest is silica which produces characteristic anatomic lesions in the lungs Clinically silicosis induces (1) a cough productive of a mucopurulent sputum (2) dyspnea

(3) pain in the chest (4) loss of weight and (5) anorexia The physical signs are similar to those observed in other fibrotic conditions of the lungs While typical silicosis is characterized by nodules disseminated throughout both pulmonic fields and asbestosis is characterized by the ground glass appearance of the lungs in a number of cases there occurs a confluent fibrosis with enlarged hilar shadows (Fig 86) These coalescent fibrotic areas have been mistaken for cancer of the lung Formerly cancer was invariably mistaken for an inflammatory condition at present the reverse often takes place (Fig 87)



Fig 86—Pneumoconiosis ( ) confluent type mistaken for cancer of the lung

Bradshaw and Chodoff reported two illustrative cases Their first patient presented symptoms and roentgenological evidence suggestive of cancer of the lung That the patient was exposed to siliceous dust for a number of years was known but not seriously gone into A thoracotomy was performed the lung removed and what grossly seemed to be a carcinoma was found histologically to be a confluent type of anthracosilicosis

Their second patient's complaints were compatible with a malignant disease of the lung a diagnosis that was entertained in three different



Fig 87 —Granuloma of right upper lobe mistaken for carcinoma The cellular reaction consists of macrophages erroneously diagnosed as cancer cells

hospitals With the bronchoscope, the lumen of the right bronchus appeared to be almost completely obliterated at the level of the middle lobe This was attributed to an extrabronchial lesion The trachea was deviated to the affected side This patient, too, had been a miner for a number of years, and, as in the first case, no particular importance was attached to this fact An exploratory thoracotomy was performed, and a large firm mass in the upper lobe was diagnosed as carcinoma, but under the microscope it was found to be anthracosilicosis with extensive fibrosis and consolidation

As can be seen the occupational history of the patient is of paramount importance in cancer of the lung as indeed in other pulmonary diseases

13

Closing Note

In the past, primary carcinoma of the lung was overlooked because it was considered a great rarity At present however the endemic spread of pulmonary cancer is widely known and physicians as a rule are familiar with the frequent occurrence of the disease as well as with the current methods of diagnosis Failure to discover cases in the earlier (operable) stages is no longer due to lack of "suspicion" on the part of the doctor but chiefly to the nature of the disease and indeed to the attitude of the patient

The early phases of cancer of the lung (as well as cancer of other organs) generally are not heralded by alarming signs or symptoms In fact it has often been stated that cancer of the lung is usually "silent" at the onset However the silence is more apparent than real

In Chapter 1 evidence was presented that pulmonary cancer generally arises in the mucosa of a large bronchus *i e* in the stem bronchus or one of the main branches and that it arises in a small bronchiole at the periphery of the lung only in about 20 per cent of cases While most peripheral cancers remain asymptomatic for an indefinite but considerable time in the central type of cancer symptoms appear rather promptly The bronchial tube in which the cancer arises as well as the tributary segment of the lung reacts promptly to the newcomer The reaction consists of a disturbance in the respiratory cycle changes in the pulmonary parenchyma and an almost instantaneous appearance of a tussive reflex This is accompanied or soon followed by a systemic reaction *i e* indispoposition and a low grade fever It has been stressed that these symptoms although mild should be treated with circumspection when they appear in persons (particularly males) of cancer age

The mildness (erroneously defined "silence") of the incipient phases of pulmonary cancer is no doubt the main stumbling block in the diagnosis at the onset of the disease Patients consult a physician many months after the onset of symptoms and they are usually opposed to suggestions or requests to undergo costly and time consuming investigations The policy of "wait and see" is no longer adhered to by the physician today but rather by the patient who is often loathe to associate his trifling symptoms with a serious illness let alone a possible cancer

Therefore the tests are usually postponed until the advent of pronounced symptoms such as blood streaked sputum hemoptysis or pain

It is well to point out that this attitude also holds true when cancer of other organs is involved It has been stated repeatedly that in clinical practice the finding of an early cancer of the cervix is a rarity "Urologists wrote Greevy are confronted by the hard fact that at least 95 per cent of patients (with cancer of the prostate) have an inoperable or unrecognizable lesion so far as cure is concerned when they are first seen

It is of interest that although cancer of the prostate (to quote one example) occurs with much greater frequency than cancer of the lungs *attention is focused chiefly on the pulmonary cancer* The success obtained in discovering early cases of tuberculosis by mass x ray surveys has prompted investigators to apply the same method in the search for "early i e operable cases of cancer of the lung The analogy however is preposterous because the concept of case finding in tuberculosis was based essentially if not exclusively on the idea of prevention Indeed the discovery of single cases of unsuspected tuberculosis was an effective measure against the propagation of the contagious disease This of course does not apply to cancer of the lung Moreover the opinion is wide spread that the mass surveys conducted by specialists have failed to uncover bronchiogenic cancer in a significantly earlier phase than that seen in ordinary medical practice As I have stated above the so called general practitioner of today is well acquainted with the riddle of *cancer of the lung The immense increase of this disease* observed in recent years is largely due to the alertness of the general practitioner and the internist who are the first to see the patient

The statement was made before that failure to discover cancer *of the* lung in its earlier phases is due chiefly to the nature of the disease and also to the attitude of the patient Since cancer of the lung is but a part of the larger problem of malignant disease its nature will not be under stood until the solution of the entire problem is at hand but the attitude *of the patient can be altered through expanded education*

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Fig 88—*A*, pulmonary artery with a hugely dilated nutrient vessel containing cancer cells *B*, cancer cells in wall and lumen of a pulmonary vein Tumor cells line the intima of the vein

The study of metastases should concern itself with

1 The propensity of the tumor to spread to distant organs
2 The route used by the neoplastic cells to reach distant organs
3 The predilection of metastases for certain organs
4 The clinical manifestations
5 The management

MODES OF DISSEMINATION

Hematogenous —The blood stream is looked upon as the essential mode of transportation of neoplastic cells to distant organs Clusters of cells probably of microscopic dimensions, enter the veins from the lymphatics, which are the first structures to be invaded Some lymphatics are believed to open directly into the veins Neoplastic cells also invade the walls of blood vessels and propagate by way of the vasa vasorum (Fig 88) Early pathological changes take place in blood vessels in the vicinity of a cancer, the veins are usually affected at the onset of the disease and the arteries at a later period As in inflammatory conditions of bacterial

s The malignant

89) pass through

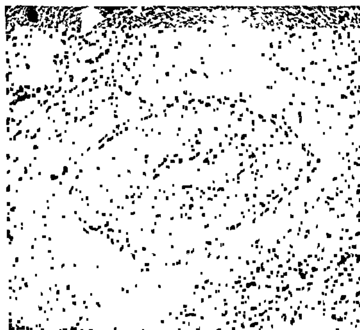


Fig 89 —A neoplastic thrombus almost completely occluding a pulmonary vein

Metastatic spread is effected along three main currents

1 The pulmonary artery—for cancer of the lung
2 The vena porta—for intestinal cancer
3 The vena cava—for extrapulmonary and extraintestinal cancers

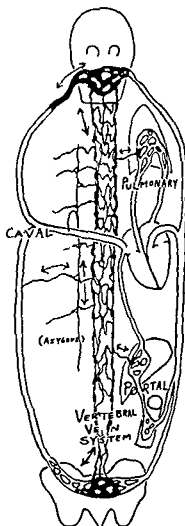


Fig 90—The system of vertebral vein as depicted by Batson (schematic drawing)

Batson by injecting opaque material into superficial veins of cadavers and live monkeys observed that metastasis is effected through a system of valveless vertebral veins These veins have free and rich anastomoses at each spinal segment with the veins of the thoracoabdominal cavity (Fig 90) With every compression of the trunk the intratruncal pressure

is raided to a sufficient height so that blood flows not into the inferior vena cava but into the vertebral veins and carries with it neoplastic cells (or bacteria)

Batson found that these intercommunicating veins are the site of frequent reversals of flow creating a pathway up and down the spine which bypasses the heart or lungs Since the pathway has many connections it provides a ready vehicle for unorthodox metastatic patterns He thus explained why the lungs are free from metastases in instances where they were present in other visceral organs

Zeidman and Buss have shown that while some cancers upon reaching the lungs via the circulation settle there and set up metastatic foci others pass immediately from the pulmonary into the systemic circulation and produce metastases in extrapulmonary viscera leaving the lungs intact

DISSEMINATION OF BRONCHIOGENIC CANCER

Cancer of the lung arises from the basal cells of the bronchial mucosa The neoplastic cells then advance toward the bronchial lumen and form an intraluminal growth which in turn leads to a narrowing and to occlusion of the bronchial orifice In many cases the cells grow around the bronchial wall causing its manifold thickening and transforming the bronchus into a rigid tube In many others they grow toward the trachea and esophagus inducing dyspnea and dysphagia (Fig 91) Finally they spread toward the pulmonary parenchyma and on to distant organs

The mode of advance of cancer of the lung varies to a great extent from one type to another The most frequently encountered squamous cell cancer advances in broad sheets or in narrow columns which produce a stroma that often leads to the tumors imprisonment and to a retardation in its progress (Fig 92) In adenocarcinoma the stroma is less pronounced and in oat cell cancers it is even less noticeable The cartilagenous plates of the bronchial walls do not impede the progress of the tumor but are usually passed surrounded or invaded Some tumors form bulky masses around the bronchus which compress its walls and narrow its lumen causing an extrinsic bronchostenosis

Although cancer cells are carried by way of the blood stream they tend to settle in some organs and to bypass others One group of observers claimed that the "favoritism which metastases display depends upon the terrain or soil on which the neoplastic emboli happen to settle They believed that some organs are inimical to the growth of neoplastic cells Another group of observers believed that the "partiality" could be adequately explained by the mechanism of circulation i e the accessibility It is unquestionable that the accessibility to invasion is of great importance However the significance of the terrain should not be

disregarded The spleen is a case in point It has been demonstrated that in the incipient phases metastatic cells abound in the spleen (Fig 93) but at autopsy splenic metastases are rarely found The heart and the thyroid which possess a rich blood supply contain fewer metastases than other organs



Fig 91 —Invasion of the trachea by cancer leading to thickening of its wall and to narrowing of its lumen

There is a considerable discrepancy between the figures published by past and contemporary observers The incidence of metastases as given by former investigators is much lower even for organs in which metastatic foci can readily be discovered e g the kidney or the liver

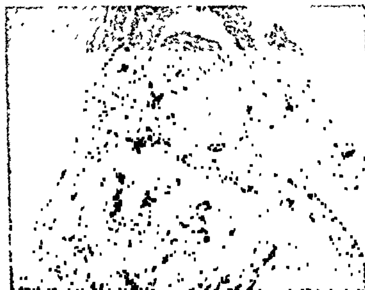


FIG. 92.—Strands of cancer cells immured in dense fibrous tissue beneath the bronchial mucosa which shows metaplasia and neoplastic transformation



FIG. 93.—Squamous cell cancer in the lumen of a hugely dilated lymph vessel of the spleen

The brain, the bones, and the *adrenals* were overlooked altogether as sites for metastases from cancer of the lung The discrepancy between the autopsy and clinical findings has been pointed out on many previous occasions, and more recently noted by Matousek in his studies at the *Walter Reed Hospital*

The distribution of metastases from primary carcinoma of the lung is shown in Table [illegible]
pulmonary cancer [illegible]
vessels which fav[illegible]
because of the protracted course of lung cancer

Table 8 Distribution of Metastases from Primary Carcinoma of the Lungs

Organ	*Per cent*	*Organ*	*Per cent*
Lymph nodes	96 00	Intestines	9 64
Bones	48 40	Pancreas	9 00
Adrenals	39 64	Thyroid	7 00
Liver	41 00	Esophagus	7 00
Kidneys	19 00	Subcutaneous tissue	5 70
Heart	14 50	Stomach	3 50
Contralateral lung	12 80		
Spleen	9 70		

Table 9 Metastases to the Heart

Authors	*Tumors*	*Metastases*	*Per Cent*
Burke	327	14	4 3
Cohen and Perry	315	65	20 6
DeLoach and Haynes*	980	137	5 7
Dimmette	455	38	8 4
Herbut and Maisel	640	35	5 4
Lamberta *et al*	1032	31	3 0
Polia and Gogol	1450	29	2 0
Pritchard	4375	146	3 4
Ritchie	857	16	1 8
Scott and Garvin	1085	118	10 9
Siegel and Young	44	8	7 4
Willis	323	20	6 2

*Macroscopic metastases only were included

1 The Heart

Incidence —Primary neoplasms of the heart are extremely rare, but metastatic ones are found in about 7 per cent of cases (Table 9)

The low incidence of cardiac metastases from the widely metastasizing extrapulmonary cancers is attributed to the rapid flow of blood through the heart to restricted lymphatic connections to the strong kneading action of the heart muscle and possibly to metabolic peculiarities

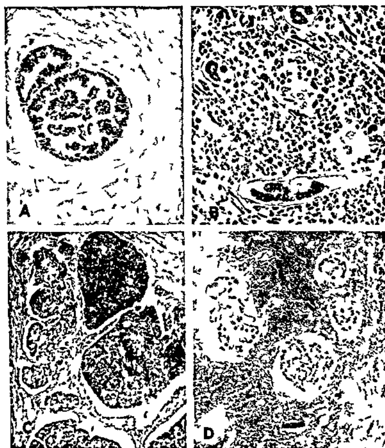


Fig 94—Metastasis to heart A cancer in a pericardial blood vessel B cancer in a myocardial blood vessel C in an epicardium D as in C

Structures Involved—Metastases are found in the atria the ventricles and the septa The endocardium and the valves are involved less often due possibly to their poor vascularity and also to their "perpetual motion" which hampers the attachment of malignant cells to their surfaces

The myocardial metastases are hematogenous and usually multiple (Fig 94) I have observed a case of a solitary metastasis to the muscle

of the left chamber of the heart. *As a rule, both sides of the heart are involved—the right side probably more frequently.*

The predominance of the *right side* of the heart was explained on a circulatory basis. Kretz, by *injecting* fluid into the coronary arteries, noted that 75 per cent of the coronary arterial flow returned to the right

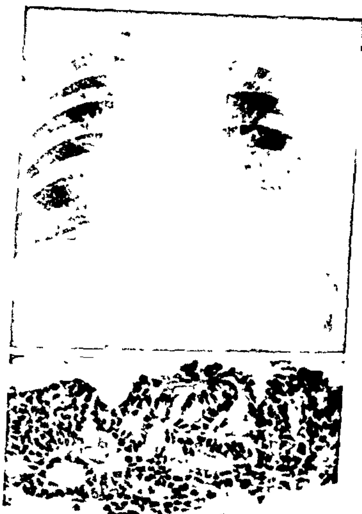


FIG. 95.—Malignant pericarditis with effusion. Cancer cells obtained from the pericardial sac by a needle puncture. Paraffin section.

chamber of the heart, passing through the thebesian veins and the coronary sinuses. It is conjectured that tumor emboli, likewise, have a greater opportunity to lodge in the right side of the myocardium.

Malignant Pericarditis.—The pericardium is invaded by tumor more often than the myocardium. In most instances it is reached by continuity,

and in many cases it produces a diffuse spread over the pericardial leaflets producing an adhesive or constrictive pericarditis Constrictive pericarditis is usually caused by tuberculosis

Pericarditis of neoplastic origin is characterized by a pericardial effusion which may be serous serofibrinous hemorrhagic or purulent If the effusion has a tendency to reaccumulate rapidly its neoplastic nature is almost certain

traumatic pericardi

pericarditis They

the heart on the character of the pulses and on the roentgenological electrocardiographic and cytological data An investigation of the cellular contents of the pericardial fluid using the same method as in pleural exudates is often sufficient for arriving at the correct diagnosis (Fig 95)

In any case of proven carcinoma particularly if it is of pulmonary or mammary origin (melanoma metastasizes to the heart with still greater frequency) the appearance of cardiac irregularities should suggest a metastasis Cardiac failure in a person with cancer which cannot be attributed to the customary etiology is in all likelihood due to metastases to the myocardium Sinus tachycardia premature contractions auricular fibrillation auricular flutter bundle branch block and complete heart block have been observed to occur in metastases to the heart The electrocardiographic pattern found in the cardiac metastases has not revealed specific features

2 The Lungs

Since virtually every cancer finds its way into the blood stream cancer cells must of necessity enter the lungs which are the points of convergence of the body Yet a relatively small percentage of cancers yield high figures of pulmonary metastases This is probably due to the property of the pulmonary tissues to destroy neoplastic cells which happen to become entangled therein It is also very likely due to inadequate investigation Metastases from some cancers proliferate rather slowly so that even at postmortem examination they are detected only with the microscope The discrepancy concerning the incidence of metastases between former and present day observers is largely due to the practice of former investigators to discard organs after gross inspection while the pathologists of today resort as a rule to a microscopic search Elkin in a study of 104 cases of carcinoma of the prostate stated that roentgenological evidence of pulmonary metastases from this organ is relatively uncommon because even at autopsy they are usually of microscopic dimensions

Core of Metastasis—The core of a metastasis is an embolus which consists of a few cells only One or multiple emboli may settle in one or

both lungs, without any predilection for a particular lobe or *segment*, or they may reach the lungs in waves As the cells proliferate, they produce new *foci*, which serve as sources for metastases to the same or to the contralateral lung and to distant organs The metastatic focus may *remain* solitary for life, growing in size only



FIG 96—Bronchiogenic cancer at the base of the right lung with lymphangiotic spread to the ipsilateral lung and a hematogenous spread (round densities) to the contralateral lung

Classification—Pulmonary metastases have been variously classified due in all probability, to the study of different phases of the process Classifications were frequently based on advanced or preterminal phases The patterns most frequently encountered are

A *The snowball or cannon ball type*, a solitary round or oval density, confined to one or both lungs When the densities are multiple, their neoplastic nature is usually taken for granted, but when the density is solitary, with no signs of malignancy elsewhere in the body, its diagnosis is beset with difficulties and can be made by means of a biopsy only

The round pulmonary lesion often described as a "coin lesion" is a primary cancer of the lung in about 30 per cent of cases The terms "snowball" and cannon ball" metastasis have been frequently used to describe the circular metastases from the kidney (hypernephroma) to the lungs However other visceral cancers provide metastases of a similar shape Metastases from pulmonary cancer to the contralateral lung often assume a round configuration (Fig 96) The roundness of the metastasis is attributed to its original growth in the lumen of the

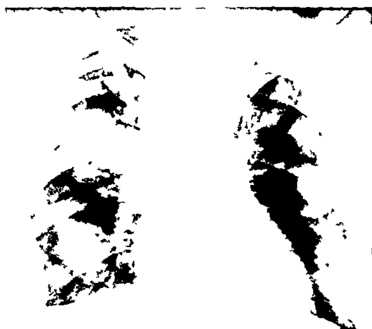


Fig 97—Metastasis to the right lung from a rectal cancer

vein from where it reached the lung Figure 97 illustrates a metastasis to the lung from a rectal carcinoma and Figure 98 demonstrates a pulmonary metastasis from a hypernephroma

B *The nodular type* of metastasis which consists of a multiplicity of roundish or angulated nodules disseminated throughout one or both lungs which probably result from a shower of emboli (Fig 99) The size of the nodules varies with the stage of the disease from 2 or 3 mm in diameter With the progress of the disease the isolated nodules coalesce and form sizable lobar masses Bronchogenic as well as abdominal cancers yield this type of metastasis Nodular metastases from a melanoma of the heel is illustrated in Figure 100

C *The pneumonia like type* of metastasis sees the air sacs filled with neoplastic cells, resembling an inflammatory exudate in pneumonia The mode of the invasion of the alveoli is not altogether clear Some observers believe that the tumor cells are brought in with the circulation *i e*, they enter the alveoli by crossing the walls of the alveolar capillaries Others state that there occurs an aerogenous invasion, *i e*, the neoplastic cells



Fig 98 —Metastases to the right lung from a hypernephroma

penetrate the respiratory portion of the lungs alongside the alveolar walls by a surface spread A pneumonia like metastasis found in the lungs of a c ... [illegible] ... na

D ... [illegible] ... tter

tosa ... [illegible] ... ney

part of the 19th century They ascertained that the sp [illegible]



Fig 99—*A* bronchiogenic cancer of the left lung with collapse of the lung *B* hematogenous (miliary) metastases to the contralateral lung Adenocarcinoma

had the opportunity of studying, occurred by way of the lymphatics They found that in the lungs, too, the lymphatic vessels were the only channels that transported the tumor (Fig 103)

However, further investigation revealed that blood carrying vessels of various calibers also participate in the process, tumor cells are invariably found in the vascular lumina and along their intimal linings (Fig 104) In fact, in these cases, too, the hematogenous route is the preferred mode of metastatic spread



Fig 100 —Diffuse nodular metastases to the lungs from a melanosarcoma of the heel

Metastatic cells from gastric cancer were found in the septal capillaries and in the larger pulmonary blood vessels, which indicates that they, too are transported by the blood stream It would appear that in these cases the neoplastic cells reach the tributary (retrogastric) lymph nodes and enter the cysterna chyli, from where they pass (via the thoracic duct) into the superior vena cava, the right side of the heart, and the pulmonary arteries It is interesting to note that neoplastic emboli pass from the thoracic duct, not only to the large veins of the neck where the thoracic duct empties, but also directly (from the duct) into the lymph

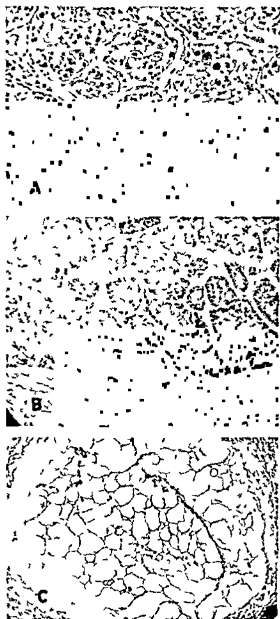


Fig 101 —A pneumonia type metastasis from a cancer of the lung The virtually normal alveolar walls must be noted B a metastasis to the lung from cancer of the liver (hepatoma) The neoplastic cells did not invade the alveoli The metastasis grew in size displacing the lung and compressing it The fine stroma of the hepatoma was imported from the liver C the stroma of the hepatoma

nodes The Virchow's node found in the supraclavicular fossa probably results from tumor emboli which follow this course

Evidence was also produced, contrary to the accepted view, that the spread of lymphangiotic cancer of the stomach is not effected by a retrograde spread from the hilus to the periphery, but by an othograde spread from the periphery to the hilus



FIG 102 —Lymphangiosis carcinomatosa spreading from a cancer of the left lung (hilus)

Manifestations of Lymphangiotic Cancer.—In lymphangiotic cancer of the stomach, the gastric lesion is usually minute and asymptomatic, i e, the patients complain of cough, rapidly increasing dyspnea, tachypnea, and cyanosis *Many succumb to failure of the right chamber of the heart* and occasionally to asphyxia (asphyxiating type) It has often been stated that *cor pulmonale* is the usual complication to which patients with lymphangiosis carcinomatosa succumb, but actually only a small percentage die of this complication The term "subacute" is applied because of the relatively short clinical course of the disease The asphyxiating type is observed in patients with widespread obliteration of arterioles, lymphatics and bronchioles In these cases there is a low oxygen saturation of the blood, a high cardiac output, and an elevated pressure in the right auricle





Fig 103.—Lymphangiosis carcinomatosa showing nests of cancer cells in the lumens of the perivascular lymphatics

Fig 104.—Lymphangiosis carcinomatosa showing tumor cells in the lumens of the perivascular lymphatics as well as within the lumens of the blood vessel

In about two thirds of the cases of lymphangiosis carcinomatosa the primary tumor is found in the stomach, and in the remaining cases it is found in the breast, pancreas, kidneys, bowel, or pelvic organs. As a rule the gastric cancer is of the linitis plastica type, and interestingly enough

it occurs mainly in young adults or in persons of early middle age. Cancer of the lung only rarely displays a lymphangiotic type of metastasis.

In many cases of lymphangiosis carcinomatosa a hemorrhagic diathesis similar to that observed in purpura or thrombocytopenia is found. In cases of carcinoma complicated by purpura a lymphangiotic type of metastasis should always be looked for.

3 The Bronchi

The bronchus where cancer of the lung originates is sometimes invaded by an extrapulmonary cancer. The metastasis is usually arrested at the mucosa which serves as a kind of barrier. In a small percentage of cases the cancer protrudes into the bronchial lumen leading to its partial occlusion which then induces cough, blood streaked sputum and hemoptysis. These symptoms are akin to those of primary carcinoma of the lung. In the presence of a nonapparent extrapulmonary cancer the diagnosis of metastasis to the bronchus requires particular alertness. It is known that bronchial biopsies as well as cytological studies by the method of Papanicolaou may be ambiguous at times.

Bronchial metastases have been observed in cases of mammary and cervical cancers but hypernephroma seems to be the tumor that metastasizes to the bronchial wall more frequently than any other neoplasm. As a rule hypernephroma produces the so called "cannon ball" type of metastasis.

Even though the tumor may protrude into the bronchial lumen (with or without ulceration of the bronchial mucosa) and regardless of whether a pulmonary mass is present or absent these manifestations alone are not sufficient evidence to allow for a diagnosis of primary carcinoma of the lung. The bronchus—dynamics as well as the state of the mediastinum—should be studied with the utmost care before radical measures are undertaken. The clinical history and the physical examination are of great significance. Of equal importance are the cytological studies of the sputum and the histological structure of the tumor.

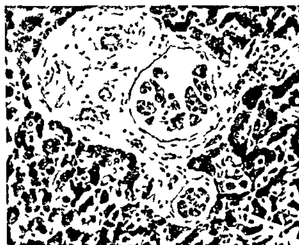
4 The Liver

The liver is rarely the seat of a primary cancer but it is frequently a target for metastases. The ratio between primary and secondary hepatic cancers is about 1 to 20. There is no cancer in the body which is not apt to set up metastases in the liver but those from the gastrointestinal tract, breasts and lungs are the ones most commonly encountered (Table 10).

That hepatic metastases from cancer of the lung are blood borne is apparent from the fact that neoplastic cells are almost always found in the intrahepatic branches of the portal vein (Fig 105).

Table 10 Metastases to the Liver

From	*Per Cent*
Colon	58.00
Pancreas	51.60
Breast	51.00
Ovary	48.00
Rectum	46.00
Lung	45.00
Stomach	41.00
Kidney	24.00



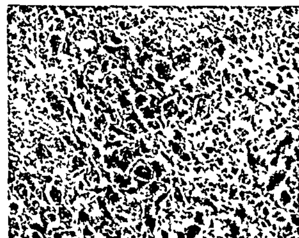


Fig. 105.—Clumps of cancer cells in the portal circulation of the liver

Fig. 106.—Intrasinusoidal infiltration by anaplastic cancer cells

The metastases may be solitary or multiple, they may be confined to the surface or buried within the hepatic parenchyma In rare instances they are lodged in the intrahepatic sinusoids without producing a gross mass The sinusoids are packed with neoplastic cells that compress the polygonal hepatic cells and gradually obliterate them (Fig 106)

Voluminous metastases usually result from the snowballing of one small mass, or from the coalescence of several small masses The liver containing metastases is usually enlarged and tender to pressure

Diagnosis —When a metastatic nodule is on the surface, it may be readily palpated but when it is seated within the parenchyma it escapes detection The enlargement and tenderness of the liver are highly suggestive, but conclusive evidence is obtained through a biopsy only

Laboratory tests —A steadily enlarging solitary metastasis usually does not cause noticeable disability or disturbance in the hepatic function There often occurs a compensatory increase in the function of the uninvolved portion of the liver The laboratory tests most commonly used i e the icteric index, cephalin cholesterol flocculation, thymol turbidity, serum alkaline phosphatase and bromsulphalein retention, may indicate changes caused by diffuse damage of the cells of the hepatic parenchyma due to toxic or mechanical factors They may also be caused by the obstruction of the extrahepatic ducts and, possibly, by circulatory disturbances The tests are often revealing and of great importance, particularly in conjunction with the clinical data The possibility of concomitant skeletal metastases yielding laboratory results of a quasi similar nature should not be forgotten

Needle biopsy —A needle biopsy has been widely used with satisfactory results (Fig 107) The test rarely fails in diffuse involvement of the liver, but it often yields disappointing results in solitary and deep seated lesions Nevertheless, it should be resorted to whenever a major surgical procedure is contemplated, also, in instances of a differential diagnosis between an inflammatory and a neoplastic process The patient should be suitably prepared and observed for 1 or 2 days after the operation The procedure is simple and generally harmless Complications are rare and have occurred in less than 1 per cent of cases They consist chiefly of pain, intrapleural hemorrhage (when the transdiaphragmatic route was used) bile peritonitis, and hemorrhage from the liver In a review of over 2 000 cases Zamcheck found a mortality of less than 1 to 1 000

Radioactive iodine —Sirret found radioactive isotopes to be a reliable method for detecting hepatic metastases The method consists in the use of radioactive, iodinated, human serum albumin as the tracer agent, and in the use of scintillation counter to detect gamma radiation from the radioactive iodine (I^{131}) The patient receives a single intravenous dose of 300 millicurie of the radioactive albumin and 24 hours later a

survey is made to coordinate points over the thorax and abdomen The values obtained are expressed in terms of per cent of an arbitrarily chosen reference point A value at a particular point higher than that which would be expected from results obtained in a series of 20 carefully selected control patients is interpreted as being indicative of a neoplastic growth The smallest metastases detected by radioactive survey were about 2 cm in diameter

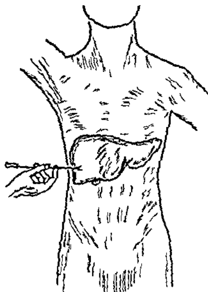


Fig 107 —Needle biopsy of liver

The method is said to be safe and accurate provided the patient is free of ascites intra abdominal and intrahepatic inflammatory lesions It has been suggested that the method be used routinely on patients with suspected carcinoma and in the follow up examination of these patients after surgery

5 The Bones and Bone Marrow

Bones—Universal Target —The bones are a target for almost every cancer of the body but above all for cancers of the prostate breast thyroid and lung Although statistics have been compiled from autopsy records figures with reference to incidence vary from one investigator to another For instance for prostatic cancer Hubeny and Mass found 35 per cent of skeletal metastases Copeland 40 per cent Turner and

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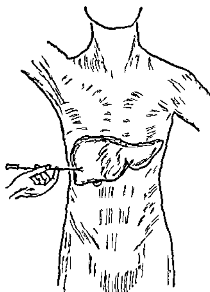


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Jaffe 57 8 per cent and Abrams 84 per cent The divergence is still more striking for mammary cancers *i e*, 30 21 57 and 73 per cent respectively (Table 11)

According to Bachman the incidence of any autopsy series depends in part on the number of bones routinely examined and the detail of the examination

Table 11 Metastases to Bones from Non pulmonary Cancer

From	*Stein per cent*	*Copland per cent*	*Hubeny and Mass per cent*	*Turner and Jaffe per cent*	*Abrams per cent*
Prostate		40 0	35 0	57 8	84 0
Breast		30 0	21 0	57 01	73 0
Thyroid		2 0	42 0	37 5	50 0
Lungs					32 5
Bladder			17 5	13 0	26 0
Kidney		6 0	21 2	20 0	23 0
Uterus		1 0	13 6		22 0
Pancreas	3 57		4 3	6 3	15 0
Rectum	5 93		0 62		12 0
Stomach	2 65	2 0	1 2	7 4	11 0
Colon	0 93	1 0			11 0
Ovary			2 5	6 0	9 0
Esophagus	2 94		8 4	1 8	2 0
Liver			11 5		
Gallbladder	16 66				
Nasopharynx			20 0	35 0	
Testes			25 0	20 0	

Blood Borne Invasion —Similar to other organs the bones are reached by cancer via the blood stream

The skeletal metastases may be (1) intratrabecular where the tumor grows in the marrow spaces between the trabeculae (2) osteolytic (Fig 108) where the trabeculae become demineralized and are replaced by the growth (3) osteoblastic (Fig 109) where the tumor cells stimulate the deposition of calcium so that the bony trabeculae increase in thickness become fused and ultimately form dense compact areas containing a sparce number of neoplastic cells within them or (4) mixed metastases where osteolytic and osteoblastic metastases are combined The localization of prostatic cancer in the bones of the pelvis in the femur and in the vertebral bodies were explained on the basis of Batson s concept of the vertebral venous system

From Lung Cancer —In the male the most frequently found skeletal metastases are from the prostate gland in the female from the mammary gland The incidence of metastases to the bone from pulmonary cancer

Table 12 Metastases to Bones from Pulmonary Cancer

Authors	*Per cent*
Stein and Joslin	15.0
Koletsky	19.0
Ochsner and DeBakey	21.0
Jaffe	22.0
Arkin and Wagner	28.0
Mattick	29.0
Rosedale and McKay	32.0
Fried	40.0



Fig. 108.—A well-circumscribed (punched out) defect in bone caused by a metastasis from cancer of the lung. In the inset is a metastasis to the rib from a cancer of the thyroid. In both cases the metastases are osteolytic.

is about equal in the male and female (Table 12). Adenocarcinoma of the lung invades the bones with considerably greater frequency than other types (Fig 110)



FIG 109—Osteoplastic metastases to the pelvis and to the femur from carcinoma of the breast

The liver, the adrenals, and the bones are almost equally affected by metastases from pulmonary cancer The spinal column is probably the site most frequently invaded Young and Funk stated that "the spine is a reservoir for metastases arising from any part of the body." In 74 consecutive patients who died of neoplasms, they found evidence of metastases in the spine in 41 per cent A roentgenological study of 30

spines removed by them revealed tumor in 13, or 43 3 per cent The next site most frequently invaded is the ribs The sternum ilium, scapula, clavicle, humerus, and skull are much less frequently invaded



FIG 110—Metastasis to the bone from a mucocellular adenocarcinoma of the lung

A lytic metastasis to the femur, resembling a punched out lesion caused by a myeloma, is illustrated in Figure 108 and a similar lesion in the rib from cancer of the thyroid is shown in the inset

Bone Marrow —The theory hitherto entertained that the bone marrow is deprived of lymphatics has been recently questioned but no convincing evidence to the contrary has yet been produced Be that as it may metastases primarily invade the marrow from where they spread to the bone proper The incidence of metastases to the bone marrow

Table 13 Metastases to Bone Marrow

From	*Number of cases*	*Metastases*	*Per cent*
Breast	14	8	57 14
Prostate	39	21	53 85
Lung	14	6	42 85
Stomach	13	4	30 77
Kidneys	7	1	14 28
Colon	*3*	*3*	*100 00*

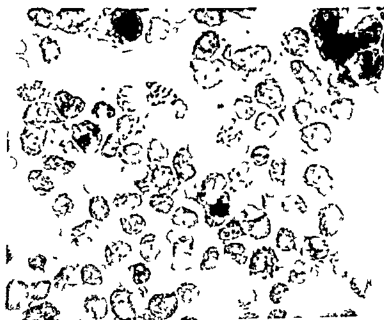


FIG 111 —Cancer cells in the bone marrow obtained by a punch biopsy

parallels that of the bone which as stated above is high for cancers of the breast lung prostate, and thyroid Figures obtained by Jonsson and Rundles are reproduced in Table 13

Although the number of their cases is limited the findings are significant Lower figures obtained by other observers may be due

to an inadequate investigation or possibly to faulty technique Repeated attempts are often necessary in order to disclose a metastatic focus (Figs 111 and 112)

Jaimet and Amy stated that they were "finding increasing evidence of cancer in a large number of patients who hitherto resisted diagnosis by means other than a bone marrow puncture They consider such a puncture to be a valuable aid in diagnosis particularly in obscure cases



Fig 112 — A orous p ol fer t on of r t ci lum cell of bone marrow B n yel cytes n the bo e marr in a case of mul ple n lo a

The search for tumor cells in bone marrow is of importance in cases where the diagnosis of a neoplastic disease cannot be established by other means. It is well known that x-rays fail to disclose skeletal metastases in a fairly large percentage of cases. At postmortem Bachman and Sproul examined the spines of 59 patients who had died of carcinoma. They observed that in more than half the cases showing metastases pathologically, the roentgenograms failed to show abnormalities. Of the 59 cases studied, metastases were found pathologically in 31, but not in the remaining 28. Of the 31 cases with documented metastatic deposits, the radiographs were positive in only 15 instances. In most of the cases the roentgenograms of the removed vertebral segments appeared entirely normal.

The early diagnosis of a metastasis is of importance when a serious surgical procedure is being contemplated. It is likewise useful in the control of hormonal therapy, e.g., in cancer of the prostate. The pathogenesis of anemias in some cancers, hitherto vaguely understood, has been intelligently interpreted in the light of studies of metastases to the bone marrow.

6. The Adrenals

The adrenals are targets for metastases from almost every cancer of the body, but mammary and pulmonary cancers reach them most frequently (Table 14). From Table 14 it will be seen that these cancers

Table 14. Metastases to Adrenals

Organ	*Per cent*
Breast	41 30
Lung	40 00
Kidney	21 00
Stomach	18 10
Pancreas	17 40
Ovary	14 90
Colon	11 20
Rectum	9 36

metastasize to the adrenals in about 40 per cent of cases. The reason is not understood, unless it is related to the usual tendency of these cancers to metastasize widely. The high incidence of adrenal metastases, as compared with metastases to the adjacent kidney (which is a much

settle primarily in the medulla, from where they

cortex suggested to Onuigo that the adrenals are probably reached by cancer cells via the lymphatics It is well known that metastases settle in the center of the lymph nodes (which are of course invaded by way of the lymphatics) from where they spread toward the periphery via the efferent vessels Again the reason for this "partiality" remains obscure unless local (the soil) or systemic factors or both are at play

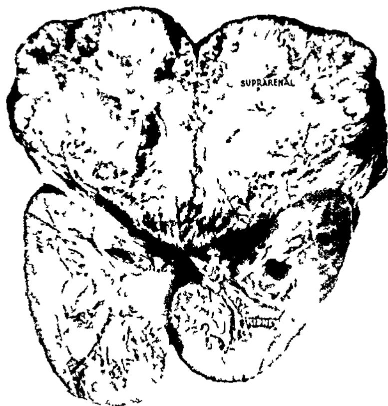


Fig 113—Destruction of the adrenal gland by a metastasis from cancer of the lung

Adrenal metastases occur on the side of the lung cancer in about two thirds of cases and in the remaining cases the metastases are either contralateral or bilateral The ipsilateral metastases are invariably larger than the contralateral ones Usually several cancer nodules of various size are found but complete destruction of the adrenals (as occurs in tuberculosis) has rarely been observed in cancer

Fig. 114.—A cerebral metastasis

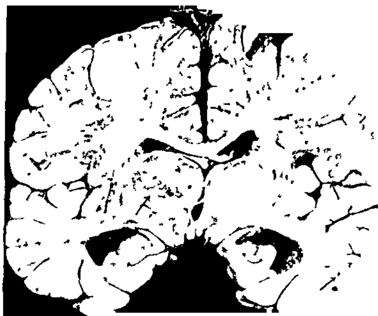


Fig. 115.—Multiple metastases in the cerebrum, also cancer in the thalmus

7 The Central Nervous System

Mode of Spread.—Similar to visceral organs, the brain is reached by metastatic malignant cells via the blood stream. This is inferred from (1) the predominant localization of metastases in the cerebrum (Figs. 114 and 115)—which is the direct arterial route to the intracranial space by way of the internal carotids; (2) the tendency of the metastases to settle in the parieto-occipital region, i.e., in the terminal branches of the middle cerebral artery where neoplastic emboli apparently lodge; and (3) the failure to identify lymphatics in the central nervous system (this *requires further investigation*).

Incidence.—The figures pertaining to the incidence of intracranial metastases from visceral cancers vary from one author to another. Courville stated that 13.5 per cent of all intracranial tumors are metastatic, while Stortebecker found 3.5 per cent, and Knights in a study of 6,500 autopsies found only 1.45 per cent.

Of particular interest is the incidence of intracranial metastases from lung cancer which was overlooked by observers in the past. For example, Krasting in an investigation of 12,000 autopsied cases with cerebral metastases from various organs failed to mention lung cancer as a source. Of 808 cases of cancer of the lung culled in 1930 by Miller and Jones, 77, or only 9.5 per cent, showed intracranial metastases. Of 47 cases with primary carcinoma of the lung reported by me in 1932, 16, or 34 per cent, revealed intracranial metastases (Table 15).

Table 15. Cerebral Metastases from Lungs and Abdominal Viscera

Organ	*Authors and number of cases*			
	Eldridge and Balsam	*Baker*	*Hare and Schwartz*	*Globus and Meltzer*
	79 cases	*87 cases*	*100 cases*	*33 cases*
Bronchus	20	24	42	19
Breast	14	24	23	
Stomach		4	3	1
Intestines	4	8	[illegible]	5
Kidneys	4	9	2	1
Adrenals		6	2	1
Thyroid	3	1	2	4
Uterus	1	5	1	
Ovaries	1	1	1	
Prostate	3	1	1	1
Unknown		4	16	1
Doubtful	29			

The reason for the great frequency of intracranial metastases from lung cancer, which is approximately 25 per cent, is most likely due to accessibility An embolus from a lung cancer may pass from the pulmonary vein and heart directly into the general circulation, and then to the cerebral circulation, whereas an embolus from a cancer elsewhere in the body (on its way to the central nervous system), becomes arrested in the lungs, where it is often destroyed It is true that a visceral cancer may bypass the lungs making use of the system of the vertebral veins (Batson), or it may enter the systemic circulation immediately upon reaching the lung, without getting a foothold in the pulmonary parenchyma 'Paradoxical' metastases are, however, rarely encountered

8 Miscellaneous

There is probably no organ which is not occasionally affected by a metastasis Metastases have been discovered in the parathyroids, the pituitary gland the stomach, the small and large intestines the breasts, the ovaries, the Fallopian tubes, and the testes In a case of a testicular metastasis, one testicle was firm, greatly enlarged and tender, resembling a seminoma It was removed and on histological examination, was found to be a squamous cell carcinoma which had metastasized from the lung The error in diagnosis occurred because the lungs were not investigated prior to the surgical intervention It is imperative that no major surgical procedure be executed without a preliminary roentgenological examination of the lungs *In fact, the lungs should be examined routinely on every hospital admission*

Metastases to the skin, which occur in about 3 to 4 per cent of cases are of particular interest because of accessibility A few nodules the size of a small wart are usually found on the chest Unless thoroughly examined by palpation (which *is rarely practiced*), they will pass unnoticed They do not signify approaching exitus, and sometimes they present the first evidence of cancer They are brought to the skin via the blood stream, and it is remarkable that they form so few foci The subcutaneous tissue is apparently not a favorable ground for a metastatic cancer

Chapter 7

Metastatic Manifestations

In Chapter 5 the pulmonary manifestations of cancer of the lung were dealt with. This chapter will be devoted to the manifestations provoked by metastases to the bones and to the brain. The symptoms produced by metastases to these organs are of particular importance because of (1) their frequent occurrence and (2) the fact that the disease often starts with osteological and neurological complaints the source of which is overlooked.

Heretofore manifestations caused by skeletal and cerebral metastases were regarded as rare and atypical for cancer of the lung. However close observation revealed that they are just another characteristic manifestation of the polysymptomatic disease.

A case of Addison's syndrome—produced by a metastatic destruction of the adrenals—is presented because of its clinical interest and also to stimulate interest in this condition which is probably less rare than generally believed.

SKELETAL

Symptoms.—The frequency of metastases to the bones from cancer of the lung makes it imperative that physicians familiarize themselves with their manifestations. It is of the utmost importance to know that symptoms may appear abruptly as the sole manifestation (Fig 116). In any case of a suspected metastasis to the bone the lungs should be investigated for cancer. The vertebral bodies are the ones most frequently invaded. Next in frequency are the ribs, the pelvis, the femurs, the humeri, the sternum and the calvarium.

Pain is an early and a quasi constant symptom. When the vertebrae are involved the pain is usually radicular, limited to certain dermatomes and aggravated by motion, cough or straining. The distribution of pain in spinal metastases and spinal arthritis is quite distinct. In arthritis the painful root zones cover wide areas and include several dermatomes, while the radicular pain associated with early metastases to the vertebra is confined to narrow zones and limited to one or two roots. Metastatic carcinoma may induce low back pain and symptoms characteristic of sciatica. In a patient of cancer age who complains of back pain the possibility of a metastatic cancer to the vertebral column should be considered.

Spinal metastases may imitate lumbar disc syndrome, and simulate the symptoms of multiple myeloma Metastases to the lumbosacral spine cause pain in the legs from pressure on nerve roots Patients are usually treated for 'neuritis" or "rheumatism," while the malignant dis



Fig 116—Mucocellular adenocarcinoma of the left upper lobe The tumor the size of a walnut metastasized to D-11 and D-12 and to the right clavicle

ease remains unsuspected Cancerous infiltration of a vertebra with fracture and collapse of the vertebral body may cause compression of the cord, leading to vesical and intestinal disturbances Treatment should be instituted promptly When paraplegia occurs, therapy is of no avail

Metastases to bone from bronchiogenic cancer are predominantly osteolytic In some instances they are mixed *i e* osteolytic in one bone and osteoplastic in another When the osteolytic metastases are extensive and rapidly progressive they induce a hypercalcemia Pain at the site of invasion and tenderness to pressure are the best signs of their presence While chemical studies of the blood and urine are helpful in the differential diagnosis a study of the bone marrow obtained by sternal puncture usually points to the correct diagnosis

Treatment of skeletal metastases from the breast and the prostate has been revolutionized by the use of hormones *i e* androgenic in breast cancer and estrogenic in prostatic cancer The treatment of metastases to the bones from bronchiogenic cancer consists chiefly in radiation which leads to the alleviation of pain in a large percentage of cases Nitrogen mustard too is often beneficial

Illustrative Cases

loss of weight

On roentgenological examination a tumor was revealed in the right femur and hip joints with a pathological fracture of a hip joint An area of density was found in the lung and was interpreted as a metastasis from the bone The fracture healed and the patient was discharged A week later she entered another hospital where analogous findings were recorded An effusion was discovered in the right pleural cavity and was attributed to a metastasis to the lung and pleura In a third hospital to which she was admitted 2 months later a diffuse thickening of the right pleura and fluid in the axillary region was found When the fluid was removed a mass 5 cm in diameter was disclosed in the right paratracheal region There was deformity of the right femur and thigh but the hip was not tender and the mobility of the joint was nearly normal

Roentgenological examination showed irregular rarefaction in the bones of the pelvis and of the right femur There were

upper lobe of the right lung The woman died after three weeks in the hospital

Necropsy revealed a right bronchiogenic carcinoma with metastases to the regional lymph nodes pericardium liver adrenals ovary and femur (Fig 117)

Comment—The pulmonary and skeletal symptoms occurred simultaneously It is remarkable that the skeletal metastases were mistaken for a primary osteogenetic sarcoma that had metastasized to the lung



Fig 117 —Metastasis to bone

Case 8 History—The patient a male 56 years of age complained of pain in the neck which had started about 3 weeks previously The pain radiated toward the right shoulder and right arm Motion of the shoulder was very painful and restricted but there was no weakness in the hand Roentgenological examination of the neck was reported to reveal a dislocation of the cervical vertebrae

Examination showed a well nourished male whose head was deviated to the left All neck motions were restricted The lungs and heart were without disease

Roentgenological examination of the cervical spine disclosed the destruction of almost the entire body of the fourth cervical segment with an accompanying anterior subluxation The inter space between the C-3 and C-4 were obliterated and the pos terior axillary portion of the fifth rib was eroded In the skull there was a small opacity above the floor of the anterior fossa

Examination of the chest revealed a fusiform pleural density in the axillary portion of the right chest There was a moderate increase in the pulmonary markings

The patient was treated by a Glisson sling immobilization followed by the application of a leather brace Radiotherapy was also used

The autopsy revealed an anaplastic carcinoma of the lung with metastases to the lymph nodes and to the cervical vertebrae

Comment—*The localization of the metastasis is noteworthy* In dis cussing the tendency of metastases to "choose" an organ or structure it is surmised that two factors are at play (1) accessibility of the neoplastic cells (2) the organ in which the metastases lodge Blood carried cancer cells settle by preference in the bones of the adult where red marrow is present The "partiality" of the cancer toward the cer vical vertebrae can hardly be explained on these suppositions alone

As in other cases pain was the first manifestation The importance of this symptom cannot be over emphasized

Case 9 History—The patient a male 46 years of age was admitted to the hospital complaining of pain in the left groin of 5 weeks duration Except for a chronic cough productive of a greenish white sputum he was in good health Four years prior to his hospitalization he sustained a chest injury which caused a fracture of the seventh rib posteriorly A few months later when pain developed in the area of the fracture an inter costal nerve was removed from a callus Two years postopera tively pain recurred in the area but a surgical intervention re vealed no abnormalities However roentgenological examination of the lungs showed a focus of dense tissue in the right lower lobe It also showed a pleural effusion that was regarded as a post operative complication The pain in the groin mentioned

suffered considerable pain when moving his legs There also was pain upon pressure over the iliac crests and the lumbar vertebrae The base of the left lung showed moist rales and expiratory wheezes which did not clear on coughing

An anteroposterior view of the chest was described as negative as were views of the abdominal viscera Except for the alkaline

phosphatase which rose to 13 the laboratory findings were non contributory

Th

c

i

on the left side A biopsy in the region of the iliac crest disclosed an anaplastic carcinoma Although it suggested an intestinal source studies of the large bowel were negative Finally 3 months after admission another x ray was taken which showed a posterior basal mass in the left lung Bronchoscopy was then performed and this disclosed a tumor in the apical division of the left lower lobe bronchus A biopsy and a cytological examination by the method of Papanicolaou confirmed the diagnosis of an anaplastic carcinoma Metastases were found in the right humerus in the left femur in the pubis and in the fourth and seventh ribs anteriorly The patient ultimately had a hemoptysis and the entire left lung was replaced by tumor However the thoracic symptoms remained mild

At autopsy an adenocarcinoma was found in the left lung metastatic to the lymph nodes the liver the adrenals the bones the brain and the skin

Comment —In this patient too the symptoms were initiated by skeletal metastases Although histologically the cancer in this case seemed to be less malignant than the cancer of the preceding case it nevertheless invaded many bones in addition to the brain the liver the adrenals and the skin Pain was the earliest complaint The pulmonary symptoms became manifest at a later date and were overshadowed by the skeletal metastases

SPINAL CORD

The spinal cord is rarely invaded by cancer The condition is primarily one of a skeletal metastasis There usually occurs an invasion of the vertebral bodies followed by an epidural compression of the cord (Fig 118)

Symptoms due to epidural compression may appear abruptly or they may develop gradually Very often they are the first and only manifestation

Illustrative Case

Case 10 History —Two years prior to admission to the hospital the patient a male 60 years of age underwent a 2 stage suprapubic prostatectomy A histological examination of the removed prostate showed fibroadenoma He remained well until about two months before the present hospitalization when he developed

weakness in both legs. Examination showed a bilateral Babinski, markedly active knee and ankle jerks and absence of the lower abdominal and cremasteric reflexes. A lumbar puncture showed a complete subarachnoid block.

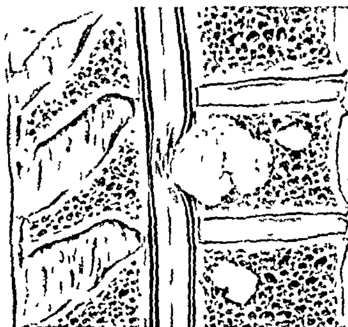


FIG. 118.—Metastases to the vertebrae from cancer of the breast. The cord is compressed by the extradural metastasis. (Courtesy The Ciba Collection of Medical Illustrations, Vol. I.)

It was conjectured that the block was due to a metastasis to the cord from a prostatic cancer which had been overlooked at the previous prostatectomy. Cisternal lipoidol injection showed obstruction at the level of the tenth thoracic vertebra. The tenth, eleventh and twelfth neural arches of the spine were removed. The bone was found to be invaded by cancer. Tumor was also found in the epidural but not in the intradural space. The patient showed slight and short lived postoperative improvement. He suffered from pain in the spine, could not walk, and gradually lost weight and strength. He died 5 months after entry into the hospital.

At autopsy an anaplastic adenocarcinoma was found in the left upper bronchus with metastases to the lymph nodes, the vertebrae, the femur, the ischium and the trachea. The cord was

compressed at T-10 but the substance of the cord was free from tumor A small pulmonary tumor was located in the vicinity of a fibrocaseous tuberculous focus

Case 11 History—A woman 54 years of age complained of pain in the lower back *She was admitted to a hospital where* physiotherapy afforded relief but the pain soon recurred with greater severity particularly in the sacroiliac region She developed anorexia and loss of weight Roentgenological studies of the sacroiliac and lumbar regions revealed atrophic changes Examination of the viscera showed no abnormalities

About 7 months later she developed paraplegia The following day she became incontinent a condition which lasted only a few days She had a *flaccid paralysis of both legs slight ataxia of* right finger to nose and tremor of right extended hand She complained of diffuse pain in both the abdomen and the lumbar spine The impression was that an extramedullary lesion of the *cord was present possibly due to a metastatic carcinoma*

Roentgenological examination of the chest showed an area of consolidation in the apex of the left lower lobe The outer half of the right clavicle and the body of the eleventh dorsal vertebra showed destruction characteristic of metastatic carcinoma The patient died after a week in the hospital

Necropsy revealed a cancer on the anterior surface of the left upper lobe Metastases that had caused *compression myelopathy* were found in the dorsal vertebrae The tumor was an adenocarcinoma with mucous formation

Comment—As mentioned above symptoms usually result from compression of the cord They consist of radicular pain and tenderness to pressure in the area of involvement This has been dealt with in some detail in the early paragraphs It is well to reemphasize that when a *person of cancer age complains of persistent pain it is an ominous symp*tom and the cause should be investigated with the utmost care Vesical and intestinal disturbances are subsequent manifestations as is paraplegia In some cases the disease is ushered in with both vesical symptoms and paraplegia

The diagnosis presents no undue difficulties A roentgenological examination is performed routinely but a negative finding does not necessarily exclude a vertebral metastasis Bachman in a study of 59 cases of malignant disease found 31 which contained metastases in the bones Only 15 of the 31 were positive roentgenologically

A lumbar puncture with the *Queckenstedt test is* helpful* The level of the block is best determined by a myelogram

*An increase in the pressure of the cerebrospinal fluid will *result from* an increase in the venous pressure in the jugular veins

Treatment (decompression) should be instituted before the occurrence of paraplegia In the paraplegic the treatment is only rarely beneficial Other therapeutic procedures e g, radiation and nitrogen mustard, bring palliation in many cases

ADRENAL GLAND

In Chapter 6 it was stated that metastases may involve one or both adrenals They may be visible as solitary round nodules or they may infiltrate the organ diffusely (Fig 119) Sometimes they attain an



Fig 119—Diffuse infiltration of adrenal gland by metastasis from cancer of the lung

enormous size as is demonstrated in Figure 113 However only rarely do they destroy both glands completely possibly because of late appearance so that patients succumb before the cancer has absorbed the entire gland

Usually the symptoms are vague and their presence may only be conjectured (lowering of blood pressure weakness out of proportion to the primary tumor and traces of pigmentation) In a few instances however cases have been observed in which the glands have been destroyed completely inducing Addison's syndrome

Addison in his original reports stated that in 4 out of 11 cases the disease was caused by metastatic cancer However critical evaluation of his material revealed that the data which he furnished were insufficient Of the 2 cases reported by Poynton Wright and Laurent 1 is proved of the 4 cases described by Wallace Buttetly and their associates only

probably less rare than the reports would have us believe

Although mammary cancer metastasizes to the adrenals about as frequently as pulmonary cancer, only the latter was found to have induced the clinical syndrome of Addison's disease by completely destroying the adrenal glands

Hitherto, the diagnosis of hypoadrenalism caused by metastases was not made during life. In Chapter 5 I quoted Matousek, who, at the Walter Reed Hospital, analyzed the records of 400 patients with bronchiogenic cancer. In none of the 81 instances of metastasis to the adrenals was a diagnosis made during life. My observations fully corroborate Matousek's findings

Management.—Metastases in cancers from the breast and the prostate have been treated with hormones, by a combination of hormones and surgery, or by surgery alone. Some reports attest to the successful removal of a solitary metastasis from the lung. Barney and Churchill, for example, reported a case in which the lower lobe was removed for a metastatic hypernephroma, with a survival of 12 years following the operation. I have followed up several patients operated on by Cushing for a solitary cerebral metastasis from cancer of the lung. Some of them survived 3 years after craniotomy, and 1 patient survived 7 years

The matter pertaining to the surgical removal of a pulmonary metastasis was summarized by Lindskog, who stated that " . . before resection is considered for metastatic pulmonary malignancy, the primary lesion should prove to be under clinical control, a reasonable time interval should usually have elapsed after primary treatment before the detection of the metastasis, and the latter should be demonstrated as clinically solitary, or at least restricted to one lobar area "

In recent years metastases to the liver have been treated by radiation or by surgery (i e , by the removal of a hepatic lobe)

CEREBRAL

Diagnosis.—The clinical manifestations of intracranial metastases depend on the area of their localization, and on the number of metastatic foci. In most instances they are multiple. In 100 cases of cancer of the lung, Ford and King found 27 which had metastasized to the brain. Twenty of these were multiple and 7 were single. The singleness of a lesion based on neurological examination should, however, be accepted with reservation, for it is known that there are areas in the brain which are "silent," *i e*, they produce no symptoms ("blind spots"). The motor area is apparently the site of predilection for metastases, next in frequency is the occipital region. The leptomeninges and the cerebellum are invaded in a small percentage of cases (Figs 120, 121)

The patients may be divided into two groups

1 Those whose cerebral symptoms appear while they are under observation for a lung cancer (Fig 122)

2 Those whose cerebral symptoms are the first and apparently the only symptoms (Fig 123)

The diagnosis of a cerebral metastasis is relatively simple provided one is aware of the manifestations of primary carcinoma of the lung When a patient with bronchogenic carcinoma begins to show personality changes e g depression disorientation or mental psychopathic abnormalities an intracranial metastasis should be considered Conversely



Fig 120 — Meningitis carcinomatosa Cancer cells line the meninges and invade the subarachnoid space

when signs of an intracranial lesion appear in persons of middle or past middle age they should always suggest the possibility of a metastasis from the lung In both these groups the disease may be initiated with *amazing suddenness and progress with great rapidity*

In patients with sudden onset of the disease the first symptoms usually consist of (1) Jacksonian and general seizures (2) hemiplegia and (3) weakness These symptoms are due to the involvement of the motor area The disease may start with symptoms of intracranial pressure *i e* headache nausea and vomiting followed by sensory and visual disturbances Bilateral papilledema is observed in a number of patients and

in a fairly large percentage of cases there is involvement of the peripheral portions of the fifth, sixth, and seventh nerves

Chemical and cytological studies of the cerebrospinal fluid do not yield diagnostic clues. At times, there is an increase in the globulin and sugar, but tumor cells are not found (Table 16).



Fig 121.—Metastasis to cerebellum



FIG 122.—Bronchiogenic squamous-cell carcinoma of the left hilus with hoarseness as first symptom The neoplastic nature of the hoarseness was not diagnosed until the advent of a cerebral metastasis

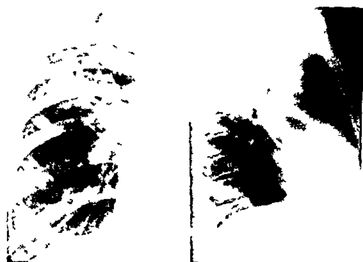


FIG 123.—A roentgenogram from a patient in whom the presenting symptom was caused by a metastasis to the brain

Table 16 —(Continued)

Case	*Sex*	*Age*	*Pulmonary Symptoms*	*Cerebral Symptoms*	*Optic Discs*	*Postoperative or autopsy findings*	*Survival*
11	F	58	None	Onset sudden with numbness and weakness of right arm and leg, aphasia and dimness of vision	Choked	Surgical removal of carcinomatous cyst from left occipital lobe recurrence of symptoms 34 months later removal of another tumor from same location	Sudden death from pulmonary embolus during recovery from 2nd operation, $3\frac{1}{2}$ years after onset of cerebral symptoms and 34 months after the first operation
12	M	56	None	Onset sudden with twitching of facial muscles, paraphasia	Neg	First exploration negative, exploration 3 months later with disclosure of tumor in left parietal lobe	Death 7 months after onset of symptoms
13	M	67	None	Onset sudden with right hemiplegia and severe occipital headaches, mental symptoms one month later	Choked	Exploration with removal of an enucleable nodule from motor area Autopsy finding of adenocarcinoma in cerebrum, cerebellum and pons	Death $2\frac{1}{3}$ months after onset of symptoms
14	M	56	None	Sudden onset with paralysis of left side of face, disorientation, dysarthria	Choked	Autopsy finding of multiple metastases in cerebrum, cerebral leptomeninges, spinal cord and along dorsal root ganglion, largest nodule in occipital lobe	Death 3 days after hospitalization

Differential Diagnosis—The differential diagnosis between a primary and a metastatic cerebral tumor is frequently baffling The most common cerebral tumor found in persons of middle or past middle age is a rapid growing *glioma multiforme* which shows early choking of the optic discs in the majority of patients However the average period of survival from the onset of symptoms is probably longer in the glioblastoma than in metastatic epithelial tumors It varies from several months to a little more than a year depending upon whether or not an operative procedure has been carried out

Similarly the differential diagnosis between an intracranial metastasis and a cerebral vascular lesion presents difficulties The progressive character of the disease with its signs of a steadily increasing intracranial pressure would make the diagnosis of tumor more plausible The same holds true of encephalitis although some degree of papilledema likewise occurs in patients with this disease

Management—The appearance of a metastasis is an ominous event, particularly if it occurs in the brain where a small lesion sometimes produces symptoms that require urgent surgical intervention Cerebral metastases are multiple in about 75 per cent of cases and solitary in about 25 per cent Their removal frequently leads to the alleviation of suffering and to the prolongation of life When the patient s condition is good craniotomy is indicated even though the pulmonary cancer is not resectable I have observed several patients who survived from 3 to 7 years following the removal of a metastasis by Cushing Ballantine and Byron reported a case where a combined attack was made successfully on a bronchiogenic carcinoma and its apparent solitary cerebral metastasis Although the consensus is that individuals with intracranial metastases do not withstand neurosurgical procedures very well in certain cases a "calculated risk" should be taken

Chao and his associates suggest palliative roentgen ray therapy for brain metastases in all patients whose life expectancy is not more than a few weeks They believe that in most cases radiotherapy is preferable to surgery because of the likelihood of multiple intracranial metastases and the frequency of residual cancer elsewhere in the brain

Nitrogen mustard and triethylenethiophosphoramide (thio THEPA) have been used in the palliation of symptoms caused by intracranial metastases with success From 40 to 50 mg of the chemical (*i e* thio THEPA) is injected into the common carotid artery in the manner used in angiography Remissions are maintained by injections of the remedy every 7 to 9 weeks It is interesting that local skin metastases respond to injections of the drug into the cutaneous tumors

In experimental studies Kramer and Schatten found that thio-THEPA was effective in reducing the number of melanoma pulmonary metastases

when administered after removal of the primary tumor Metastases were completely prevented in some animals

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Chapter 8

Diagnostic Procedures*

*The sections on Bronchoscopy Lymph node biopsy Exploratory Thoracotomy and Thoracentesis are contributed by Dr Thomas H Burford and Dr Thomas B Ferguson

BRONCHOSCOPY

BRONCHOSCOPY is one of the most important diagnostic and prognostic procedures available It should be considered an integral part of the workup in every patient with a suspicious shadow except perhaps solitary circumscribed lesions that lie far to the periphery The main objective of bronchoscopic examination is to visualize an endobronchial tumor mass and make a tissue diagnosis by biopsy This can be done only in about 50 per cent of the cases however because the bronchoscopic view of the tracheobronchial tree is limited by the anatomic configuration The trachea main stem bronchi and secondary divisions of the lower lobes can be seen clearly in the usual case but visualization of the upper lobes is usually limited to an oblique view of the main orifice Endoscopic sets with lens systems are available which permit adequate right angle visualization but these are not in general use

The fact that a tumor is visualized and a biopsy taken through the bronchoscope is advantageous from the standpoint of diagnosis but may have an ominous prognostic significance In a recently reviewed series of 501 cases of proved pulmonary cancer treated at Barnes Hospital St Louis a positive tissue diagnosis was obtained in 211 cases or 46 per cent of the 459 patients who were bronchoscoped When those with positive findings had exploratory thoracotomy only 1 case in 4 (28 per cent) had a lesion for which pulmonary resection could be done the others being nonresectable in almost all instances because of blood vessel invasion at the hilum

Other important information can be gained from bronchoscopy A careful evaluation of vocal cord function should be done before the bronchoscope is passed beyond A paralysis of either recurrent laryngeal nerve is an ominous sign and may alter the plan of treatment The left nerve is more frequently invaded A few long term survivals have been reported following resections where the recurrent nerve was involved but in the vast majority of patients it is an indication of noncurable mediastinal penetration In the Barnes Hospital series no case with recurrent

nerve involvement has survived 5 years. A widening of the carina should always arouse the suspicion of tumor metastases in the subcarinal lymph nodes or tumor permeation of the submucosal lymphatic channels. A biopsy of the carina should be taken in such cases because demonstration of tumor in this area means the lesion is beyond surgical control. If a tumor mass is present in one of the main stem bronchi it is vital that the surgeon do the examination and determine the location and extent of the lesion. He can then judge whether sufficient bronchial length is present to perform the resection and leave a bronchial stump free of tumor.

Other abnormalities may suggest the presence of a tumor which is outside direct bronchoscopic view. A firm extraluminal mass may impinge on the bronchus and cause luminal narrowing, or the normal degree of mobility of the bronchial tree as tested with the bronchoscope may be lost when the tumor mass encircles the bronchus. Blood or blood flecks may be seen coming from a segmental orifice, indicating trouble beyond.

The direct endoscopic collection of secretions from the bronchus draining an area of infiltration is an important diagnostic study. If secretions are scanty the bronchus may be lavaged with a small amount of saline, which is inhaled deep into the lung and then coughed back to the bronchoscope tip where it can be aspirated into a trap container. The secretions can then be studied by several means. A recent notable advance has been the development of exfoliatice cytology. Stains and cultures of the secretions are helpful in determining whether tuberculosis or fungus disease is present. When pyogenic infection is superimposed, sensitivity studies will lead to proper antibiotic coverage and allow earlier surgery.

In the majority of patients bronchoscopy can be done under local anesthesia with minimal discomfort if proper attention is given to a few details. Topical anesthesia should be applied rapidly and thoroughly. We feel 5 per cent cocaine solution is still the most satisfactory agent available, and if the total amount used is kept below 10 cc very few side reactions will occur. In children and some apprehensive adults general anesthesia will be required. Bronchoscopy should be performed with a definite planned procedure well in mind after study of the patient and his x ray films. The examination is done to look for certain specific changes, not merely to "look around." In experienced hands the total time of the examination, including taking a biopsy and bronchial washings, should be no more than 2 to 3 minutes. Very few patients will complain of a bronchoscopy that is deftly done.

LYMPH NODE BIOPSY

Careful inspection and palpation of the supraclavicular areas is very important in the evaluation of the lung cancer suspect, for this is one of

the first extrathoracic regions to become involved by metastatic tumor If a palpable mass is present a biopsy should be taken as a first procedure for it will yield a histological diagnosis and show the lesion to be beyond surgical help at the same time Recognizing this as an important lymphatic pathway for extension Daniels did deep cervical biopsies in patients without palpable nodes a method now known as scalene (or prescalene) fat pad biopsy The supraclavicular incision is the same as for phrenic nerve crush The entire block of fatty tissue lying on the anterior scalene muscle is dissected out and removed leaving the muscle and the overlying phrenic nerve cleanly exposed The fat pad is then dissected for nodes Connar has stressed that an adequate biopsy should yield at least 4 lymph nodes The side of the neck elected for exploration depends upon the location of the lung lesion For an upper lobe lesion the ipsilateral cervical region is explored For a lesion of the right middle lobe or either lower lobe the right side is explored This is based on Rouviere s studies on the lymphatic drainage of the lung, showing the left lower lobe drainage pathway is principally to the right paratracheal nodes by way of the subcarinal chain

Excluding patients with palpable cervical nodes the incidence of positive scalene biopsies is too low to recommend routine use of the procedure in all cancer suspects Seghers found 14 positive results in a series of 132 cases an incidence of 11 per cent Harkin has suggested the combination of scalene pad excision with superior mediastinal exploration to increase the number of positive tissue diagnoses The superior mediastinum is explored with the finger and with a lighted instrument such as a laryngoscope and a biopsy is taken of any suspicious areas In a series of 142 cases of cancer without palpable cervical nodes he found positive tissue in the cervicomediastinal areas in 45 cases or 31 7 per cent The value of this extended procedure is questioned however since patients who require a diagnostic procedure of this magnitude probably deserve an exploratory thoracotomy

EXPLORATORY THORACOTOMY

The value of exploration of the chest as a combined diagnostic therapeutic weapon against cancer is now well established If a lung malignancy can be diagnosed by one or several of the methods mentioned in previous sections it stands a reasonable chance of being non resectable or resectable with lymph node involvement If the lesion can only be diagnosed at thoracotomy and frozen section biopsy it stands a good chance of being extirpated with cure In 51 cases of cancer that survived 5 years after surgical resection reported by Overholt exploratory thoracotomy was needed to make a diagnosis in 30

With increased knowledge of respiratory and circulatory physiology

problems of fluid balance, and modern anesthesia, the risk of thoracotomy is very low. The standard maximum surgical treatment for cancer of the lung, that is, pneumonectomy with removal of the hilar nodes, was performed on the very first successful case 25 years ago, so that increasing the magnitude of surgery is not likely to improve the survival rate. Our only hope lies in the detection and resection of the malignant lesion at an earlier stage of its development.

THORACENTESIS

The detection of pleural fluid in cases of suspected lung cancer is important since metastases to the pleural membrane is generally accepted as an extension which is beyond surgical aid as far as control of the neoplasm is concerned. It is important to realize that the presence of fluid *per se* in a cancer case proven by other means does not mean that the lesion is nonresectable, even if the fluid is bloody. Pneumonitis distal to a bronchial cancer can cause an inflammatory effusion and the lesion still be resectable at operation. To be of prognostic significance, tumor cells must be demonstrated in the fluid. This can be done by cytological smear if the quantity of fluid is small, but if an ample amount is present it should be centrifuged, the sediment blocked in paraffin, and routine tissue slides prepared. True metastases to the pleura consist of innumerable implants on the visceral and parietal surfaces, which usually cause a profuse outpouring of fluid, frequently blood tinged. For this reason tumor cells are rather easily demonstrated in these cases, and if cell blocks are repeatedly negative the diagnosis of pleural metastases should be seriously questioned. In a series of 19 cases of undiagnosed pleural effusion seen at Barnes Hospital, in whom the cell blocks of the pleural fluid were negative, the clinical suspicion of cancer was strong because the average patient's age was 50, and 7 of the 19 effusions contained blood. At exploration in these 19 patients, however, only 2 cases of malignancy were found, 1 a bronchogenic carcinoma with pleural extension, and the other a malignant pleural mesothelioma.

SPONGE BIOPSY

By this method a specimen is obtained, not by snipping off bits of tissue, but by absorbing the suspicious matter with a sponge. Briefly, the technique is as follows. After a thorough bronchoscopic examination of the bronchial tree, a small segment of sponge (Gelfoam or Onko sponge), which has been attached to the sponge carrier, is introduced into the orifice of the suspected area. It is then allowed to become well soaked with the tissue secretions. On withdrawal, the sponge is fixed in a 10 per cent solution of formalin, sectioned, and stained in the same manner that sections are prepared from paraffin blocks. Under the

microscope the tumor cells are seen within the matrix of the Gelfoam sponge. Thus far sponge biopsy has yielded favorable results.

ASPIRATION OR NEEDLE BIOPSY

By this method a needle of 17 or 18 gauge caliber attached to a syringe is inserted through the chest wall directly into the neoplastic



Fig. 104.—Aspiration biopsy. Top, adenocarcinoma; bottom, undifferentiated cell carcinoma.

tissue The tissue is then aspirated by means of a strong, negative pressure The Vim-Silverman needle is considered to be the most suitable for this procedure The withdrawn tissue is then fixed in formalin and stained with the customary dyes (Fig 124)

According to some observers, this process is fraught with danger It can lead to various complications, such as, an implantation of neoplastic cells along the track of the needle, a hematogenous dissemination of the tumor cells, production of a pneumothorax, intrapulmonary hemorrhage, empyema, production of a septic air embolism, shock, and convulsions On the other hand, there are observers who find that the procedure is relatively safe Allbritten and Breckenbridge practiced it on 50 patients who were affected with diffuse pulmonary diseases, *i e*, pneumonoconiosis, sarcoidosis, metastatic malignancy, and tuberculosis They found that "it was well tolerated by the patients and produced minimal complications " Rosemond and his associates stated that "the hazards involved can be minimized if precautions are observed" They advocate the method whenever a definite diagnosis of carcinoma cannot be made by means of a bronchoscopic or cytological study From their study of 145 patients with carcinoma of the lung, Gledhill and his associates concluded that "the method can be used without serious complications" They obtained positive results in 44 out of 56 patients, or 78 5 per cent

While in my own observations I have found no serious complications in lung-cancer patients as a result of this type of biopsy, I consider it potentially dangerous and of limited value It is best employed in cases of soft, peripheral lesions, and should be done under the control of a fluoroscope I believe it should be used only as a last resort in cases where other methods have failed to yield results

THORACOSCOPY

This method, devised by Jacobaeus in 1931, calls for the insertion of a narrow, cylindrical cannula through an intercostal space An optic instrument is then introduced into this cannula so that the pleural surfaces can be inspected This process is used principally in tuberculosis cases in order to locate and sever pleural adhesion bands (pneumonolysis) that may interfere with a complete collapse of the lung

Landskog considers "the procedure to be exceedingly simple in concept, but complicated and potentially hazardous in practice " In tuberculosis, the most hazardous element is a possible infection of the pleural cavity with tubercle bacilli, which may lead to a tuberculous empyema

In lung cancer the procedure is preceded by a pneumothorax According to Edwards, thoracoscopy is of little value in cases where surgery is contemplated, 'as a removal of a portion by biopsy forceps will contaminate the pleural cavity with malignant cells and possibly infective mater-

ial from the lung" According to Burford it has no place in the diagnosis of lung cancer" (personal communication)

BRONCHOGRAPHY

The purpose of bronchography is to determine the presence of an endobronchial lesion Since the bronchi are not visible with the roentgen rays they are opacified by the injection of lipiodol of ioduron B or of dionosil These solutions coat the bronchial lining with the iodized substance thus making the bronchi visible when viewed with the x ray A bronchoscopy should always be performed prior to a bronchography

Bronchography which is widely used in cases of purulent infections of the lungs and bronchi (bronchiectasis) has a limited application in the diagnosis of bronchiogenic cancer Because of the introduction of the cytological method of studying the bronchial secretions by the technique of Papanicolaou this method has virtually been discarded in the diagnosis of lung cancer Moreover the injected lipiodol has a tendency to *persist* in the lung for a considerable length of time thereby obscuring pulmonary detail It may also on rare occasions induce a lipid granuloma The presence of the iodized oil also precludes prompt surgical intervention

Ioduron B another contrasting substance contains 60 per cent of a water soluble *radio-opaque* stable organic iodide which is known in America under the name of "iodopyracet or diodrast The iodide component is rapidly absorbed into the lung and *excreted* in the urine within a period of from 1 to 2 hours Because of its prompt elimination diodrast as as dionosil does not obscure pulmonary detail However they are more irritating than lipiodol and the picture procured is not as clear as the one obtained with the use of the iodized oil

EXFOLIATIVE CYTOLOGY

The diagnosis of pulmonary cancer by the exfoliative cytological method consists in the search for malignant cells in the expectorated sputum or in the secretions obtained from the bronchus by aspiration The test is based on the *observation* that cancer cells exfoliate from the surface *of* neoplasms and are eliminated with the expectoration (Fig 125)

Material and Method –*Sputum* –The patient is instructed *to* expectorate once from the depth of the throat (saliva is not suitable) into a small bottle containing about *30 cc* of 70 per cent alcohol The sputum so fixed *is* well preserved and therefore its study can be postponed if necessary Some observers consider that the morning expectoration is preferable others doubt whether the time of day the sputum is collected

makes any particular difference It is of greater importance to provide sputum that contains no food or other extraneous particles

To prepare smears blood tinged flecks or minute particles of the sputum are spread over glass slides in a manner similar to the technique used in the preparation of smears for the detection of tubercle bacilli



Fig 125—*A* Cancer cells (from lung cancer) in bronchial secretion (Papanicolaou technique) *B* Macrophages in lung in the vicinity of a granuloma (paraffin section)

However, the smears should be fixed promptly in a solution of equal parts of alcohol and ether Sputum that has not been fixed immediately deteriorates almost instantly and is consequently useless for study Several smears should be prepared

Bronchial Secretions —While sputum can be collected in the physician's office the collection of bronchial secretions requires hospitalization because it is performed simultaneously with a bronchoscopy



FIG 126 —Macrophages in lung in the vicinity of a chronic lung abscess (paraffin section)

The secretions are secured from an area adjacent to the neoplasm by means of an aspirator attached to a bronchoscope If the amount of secretion is scant and insufficient for study, the aspirator is washed with a small quantity (2 to 3 cc) of a normal saline solution Smears are made directly from the secretions deposited on the outer surface of the tip of the aspirator Instead of an aspirator some bronchoscopists use cotton or gauze pledgets held in a bronchoscopic forceps The suspicious spot

on the bronchus is rubbed with the attached pledgets and the mucous thus obtained is spread over the surface of a slide This method is very similar to the sponge biopsy procedure described on page 218 The smear prepared from the bronchial secretions should likewise be fixed *immediately* If the collected bronchial secretions are excessive, they are centrifuged, and the sediment is utilized for both cytological studies as well as for routine paraffin sections (Fig 126)

Comment —1 The use of the exfoliative cytological diagnostic method has been contested on the grounds that a diagnosis of malignancy can not be made from the appearance of scattered single cells alone In the past, pathologists believed that, morphologically, a malignant cell varies in no way from a normal somatic cell This view is no longer accepted by present day observers, who believe that differences are discernible under the microscope These differences generally consist in (*a*) the disproportionately enlarged nucleus of the malignant cell, (*b*) the pattern of the chromatin contents, (*c*) the unduly prominent nucleoli, (*d*) the multinucleation of the cells, and (*e*) mitoses Many other aspects can also be detected by an experienced observer.

Cells exfoliate not only singly, but in adhesive groups, or clusters This affords the cytologist an opportunity to observe the pattern of the growth which is similar to that revealed in paraffin sections "Though a positive diagnosis of a malignant neoplasm may sometimes be made on the strength of single abnormal cells," wrote Papanicolaou and Liebow, "the most conclusive evidence is usually afforded by the presence of cell clusters or small tissue fragments which give an insight into the architectural pattern of the tumor"

2 Not only are cytologists in a position to identify the malignant nature of a cell, but they are also able to ascertain the particular type of malignancy, *i e*, whether the cancer is an epidermoid carcinoma or an adenocarcinoma According to some cytologists, squamous-cell cancer can be identified in about 80 per cent of cases (Squamous-cell cancer is the most common form of cancer of the lung) Adenocarcinoma is identified with great difficulty, and undifferentiated-cell cancer (*i e*, small-cell and oat cell cancers) is even harder to recognize

3 In comparative studies one group of observers found that results obtained from the examination of exfoliated cells and of tissues obtained by bronchoscopic biopsies are quasi similar, another group found that the method of exfoliative cytology provided superior results However, this method (when the sputum alone is examined) establishes the diagnosis of the tumor alone, while a bronchoscopy reveals, not only the site of the tumor in the bronchus, but the state of the bronchus and the mediastinal structures as well Furthermore, the results obtained from a biopsy are rarely equivocal

4 Exfoliative cytology has yielded positive results in peripheral, bron-

chiolar, and segmental cancers which cannot be seen with the broncho scope and therefore are not susceptible to a bronchoscopic biopsy In a study of 13 peripheral cancers of the right lung Ackerman found no positive results in the bronchial washings but 20 per cent positive results in the sputa From the left lung he found 28 6 per cent positive washings and 13 3 per cent positive sputa

5 Whether incipient or early stages of cancer can be detected by the use of the exfoliative-cytological method remains to be seen (It is well to point out that the notion of "early cancer" is a moot question) According to Papanicolaou "growths measuring a few millimeters in diameter have been successfully detected before there was any other certain indication of their presence such as shadows on x ray examina tion or lesions visible through the bronchoscope"

6 Whether the sputum or the bronchial secretions provide the best results is a subject that is similarly debatable There is a disadvantage in using the sputum because it is composed of bronchial and tracheal cells as well as cells of the oral cavity whereas the bronchial secretions contain bronchial cells only On the other hand the collection of sputum is so simple that it can be done in the physician s office or at the patient s home and can be repeated whenever necessary The collection of bron chial secretions cannot be performed outside the hospital

Summary—When properly collected and processed the sputum and bronchial washings taken from patients with pulmonary cancer show the presence of malignant cells in from 70 to 80 per cent of cases The highest figures of correct diagnoses are obtained in epidermoid (central) cancers At the Barnes Hospital St Louis Missouri epidermoid carci noma yielded 89 2 per cent correct diagnoses undifferentiated cell carcinoma 76 2 per cent and adenocarcinoma 39 3 per cent (Burford and Ferguson) Peripheral cancers also furnish correct positive results although much less frequently False positive results occur in from 2 to 3 per cent of cases

According to Burford and Ferguson exfoliative cytology as a diag

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to correct positive bronchial biopsies in 16 per cent

At the same hospital from 1946 to 1951 there were 4 false positive reports and since 1951 there has been only 1 false positive report In

a series of 198 surgical resections, 48 were carried out with the cytological finding as the sole tissue diagnosis

However, a positive cytological finding (according to the same authors) has no prognostic implication as it does with a bronchoscopic biopsy Positive smears were obtained in 56 1 per cent of the resectable cases and 59 per cent of the non resectable cases, whereas with a positive bronchial biopsy 3 patients out of 4 were non resectable at the time of surgery

Sputum is preferable for study because it is easily obtainable and the test can be repeated at will

Any patient—particularly a male of middle or past-middle age—with pulmonary symptoms suggestive of cancer should have his sputum examined for the presence of malignant cells If the reported results are 'doubtful' or "negative,' the sputum should be reexamined 2 or 3 times at short intervals This holds particularly true if the roentgen ray examination shows a picture that suggests the presence of a neoplasm

Hemogram —In cancer of the lung the blood picture lacks characteristic features of diagnostic or prognostic significance At certain stages of the disease anemia occurs in a high percentage of cases and is attributed either to a continuous loss of blood, an uncontrollable infection, or a nutritional disturbance Myelophthisic anemia, however, is rare, although skeletal (*i e*, bone marrow) metastases in cancer of the lung are frequent and widespread The concentration and size of the erythron usually remain unchanged in the presence of extensive metastases to bone marrow Generally there seems to be no correlation between the cellularity of the bone marrow, the extent of metastatic involvement, and the anemia

It is noteworthy, however, that in cases of lymphangiosis carcinomatosa (with the stomach as the primary seat of the cancer) a hemorrhagic diathesis occurs which is similar to that observed in purpura and thrombocytopenia It is believed that it is caused by the replacement of the bone marrow by the metastatic cancer cells A quasi similar type of anemia is encountered in metastases to the bone marrow from cancer of the prostate In prostatic cancer the anemia is attributed to two factors (either separately or conjointly), (1) an extensive destruction of the bone marrow by the metastatic cancer, and (2) a hemolytic agent

Some observers have suggested that anemia develops in cancer as a result of a shortening of the life span of the red cells, others have stated that it is due to hypoferremia and still others, that it is due to a deficient [illegible]

The white cells of the peripheral blood may also be [illegible]nant disease The changes are numerical and known as leukemoid reactions A leukemoid reaction is defined as a white cell count of 50 000 per cu mm It may concern the myeloid series (a myeloid leukemoid

reaction) or the lymphoid series (a lymphoid leukemoid reaction) The leukocytic count in these cases may reach 100 000 cells per cu mm and over In the past these cases were invariably diagnosed as leukemia but studies of bone marrow have shown that a leukemoid reaction is involved not leukemia

Fahey observed 3 cases of myeloid reaction in 160 cases of cancer of the lung Henkin described a case of cancer of the lung in which the leukocytic count rose to 85 000 In a case of Jackson s the white blood count ranged between 51,250 and 116 000 with 85 per cent polymorphonuclear leukocytes

I observed a case of a leukemoid reaction in a 60 year old man with ... time of the ... the white ... cell count rose suddenly to 25 000 per cu mm 62 per cent of which were lymphocytes During the next 4 years until his death in 1954 the blood count oscillated between 25 000 and 80 000 per cu mm At autopsy the bone marrow was found to be homogenous red in color hypoplastic and showed no metastases (the calvarium sternum ribs and vertebrae were examined)

The mechanism of leukemoid reactions in cancer is not understood It is conjectured that (1) the bone marrow becomes irritated" as a result of metastatic involvement (2) toxic substances become liberated by extensive necrosis of the cancer of the adjacent tissue leading to the overproduction of the white cells (3) cancer cells produce substances which stimulate the overproduction of the white cells

A flooding of the peripheral blood with eosinophiles has been observed in cases of advanced lung cancer with widespread metastases Again the mechanism of the eosinophilia is not understood

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Chapter 9

Radiology

ARNOLD L BACHMAN, M D

Routine Radiography.—In the study of pulmonary neoplasms fluoroscopic and radiographic studies are the initial and basic examinations Under the fluoroscope the gross shape of the tumor and its position within the lung are ascertained More important, however, is the utilization of the fluoroscope in determining abnormalities of function, since it provides information as to the presence and type of pulsation of the tumor, the movement of the diaphragm, and the paralysis, if any, of the vocal cords

The routine x ray films of the chest are taken in the posteroanterior, anteroposterior, various oblique, and lateral views. These films yield permanent records for careful study in much greater detail than can be seen fluoroscopically The exact position and intrinsic characteristics of the tumor may often be determined Pleural thickening, pleural effusion, and widening of the mediastinum are well demonstrated In addition, x ray studies usually help in formulating diagnostic methods and, ultimately, in applying the proper treatment

In instances where the pulmonary density is great and extensive, or is contiguous with the mediastinum, an overpenetrated exposure film is often of considerable aid With an exposure 2 to 3 times above average, the normal lung fields become grossly blackened, and the areas of greatest density—representing the tumor or its complications—are better penetrated Their structure, too, becomes evident These studies may show cavities, calcifications, atelectases, and densities undiscernible on the routine chest x rays Whenever the opacity of the pulmonary abnormality is great, an overpenetrated film in the proper obliquity may be of considerable value

Bucky Studies.—Bucky studies of the chest are also used to great advantage in cases of large and very opaque shadows in the lung fields They can also penetrate and reveal the internal characteristics of the densities In addition, they may show calcifications within the pulmonary lesions somewhat better than the simple overpenetrated films, and in the mediastinum they give good demonstration of the trachea and the main bronchi Bucky examinations are also of immense value in studying

the spine pelvis skull etc in the search for extrapulmonary metastases

Tomography —Body section roentgenography (*i e* tomography or lam

obtained by this device which may be easily attached to the x ray tables in common use The marginal and internal characteristics of the paren chymal densities are often best visualized by this method indeed cavities or calcification within a pulmonary shadow may at times be demonstrated *only* by this examination Coalescing or superimposed densities on the routine chest films may in tomography be separated for individual evalu ation Lateral view tomographs when used in conjunction with frontal studies are of value in the elucidation of the complex shadows frequently seen in cases of pulmonary carcinoma

In addition to its value in diagnosing a parenchymal tumor body section roentgenography is of great importance in investigating the mediastinum for metastases to determine their nature and exact location In fact it is a prerequisite to determine operability in cases of proved pulmonary carcinoma

An apparatus has been developed that takes the sections in the coronal and lateral planes with the patient erect and that takes axial transverse "cuts which appear like cross sectional views on the roent genograms Such views may add the advantages of erect radiography in demonstrating fluid levels cavities and the gravitational effects on fluid in the chest In addition the axial transverse cuts may aid in demonstrating the anteroposterior relationship of pulmonary tumors and perhaps may more clearly portray mediastinal masses This method has not yet been sufficiently tested to permit a definite opinion of its value

Body section roentgenography is also used in investigating extrathoracic structures for metastases Spread to the spine and pelvis are common in carcinoma of the lung and in many instances tomograms reveal spinal metastases invisible or barely visible on routine roentgenographic studies

Kymography —Kymography is a radiographic procedure in which mo tion may be demonstrated on x ray film It is of limited usefulness in the study of pulmonary tumors and is employed most often to supplement the fluoroscopic studies At times however it may aid in distinguishing between intrinsic and transmitted pulsations in a pulmonary density whose movements are not clearly visualized fluoroscopically It may also show impaired movement of the right hemidiaphragm a sign occa sionally indicating subdiaphragmatic hepatic metastases with hepato megaly

Contrast Studies —Contrast material studies are often of vital impor tance in evaluating cases of suspected or proved pulmonary neoplasms

Evidence of spread of the neoplasm is constantly sought by determining whether there is pressure on or invasion of nearby structures Since many of the structures in the mediastinum and lungs are invisible on the routine roentgenograms they must be opacified for demonstration Barium swallow studies of the esophagus may reveal evidence of mediastinal metastases which can be shown in no other manner Contrast oil bronchography is a commonly employed procedure which often reveals the nature of bronchial lesions beyond the range of the bronchoscope

Less well known but employed with increasing frequency are procedures which opacify the veins and arteries of the mediastinum and lung Much knowledge concerning the nature and extent of a neoplasm may be obtained if it can be demonstrated that these vessels are involved

In many instances pulmonary shadows are eventually found to be metastatic deposits from extrapulmonary cancers It is then important to investigate the gastrointestinal and the genitourinary tracts as well as the gallbladder and other structures to ascertain the source of the pulmonary density

DETECTION OF PULMONARY NEOPLASMS

Minute Tumors—In order to detect cancer in the early stages routine chest x rays for asymptomatic individuals have been made almost universally available This undertaking has created a new problem for the radiologist namely the detection of small pulmonary neoplasms Under ideal conditions a nodule 2 mm in diameter may be visible in a routine radiographic examination However lesions up to 1 cm in diameter are frequently invisible A slight degree of respiratory motion for example may blur out a minute shadow Of importance also is the density of the lesion—a small calcific nodule will stand out much more clearly against the aerogenous pulmonary background than a "soft" infiltrative nodule of the same size Sharply marginated nodules are more easily visualized than lesions whose borders tend to fade gradually into the surrounding lung field Since much of the pulmonary area is obscured by the ribs the faint density of very small lesions is also obscured by the osseous shadow of an overlying rib Finally the minute pulmonary shadow may be obscured by adjacent vascular markings This is particularly true where there are lesions in the juxtahilar or mediastinal areas

Even when a 2 to 3 mm nodule does appear on the radiography its nature may still be overlooked or not properly interpreted Among the causes of such misses are (1) the short time alloted for study of each film (2) fatigue affecting the reader of the film and (3) poor film quality Still another cause for failure is the common use of photofluorographic equipment These apparatuses yield films varying in size from 35 cm (for projection) to 70 mm to 4 by 5 inches Minute lesions

discernible on the large 14th by 17th inch films are invisible on the smaller radiographs

In fact regardless of how aware of the problem the examiner is and regardless of the many precautions he may take it is certain that he will overlook or improperly interpret an occasional nodule representing an early incipient carcinoma Separate viewing of the radiographs preferably by two competent observers or by the same observer on two different occasions may yield a higher percentage of correct findings

IDENTIFICATION OF PULMONARY NEOPLASMS

Variety of Patterns —The detection of an abnormal shadow on the chest roentgenogram immediately imposes the problem of its identification Pulmonary carcinoma occurs in a variety of forms and may closely resemble a number of benign tumors or non neoplastic lesions

factory approach to an adequate understanding of the various appearances of pulmonary neoplasms

1 Primary site of the tumor (*a*) root bronchus (*b*) large to medium size branch bronchus (*c*) small bronchus (peripheral) (*d*) bronchioles

2 Character of the tumor (*a*) infiltrative (*b*) fungating into bronchial lumen (*c*) nodular (pseudocircumscribed) (*d*) cavitary

3 Secondary changes caused by (*a*) complete bronchial obstruction (resulting in atelectasis) and incomplete bronchial obstruction (resulting in obstructive emphysema) and (*b*) infection (leading to pneumonitis lung abscess and pleural effusion)

4 Metastases or extension of the tumor in (*a*) the lung (*b*) the pleura (*c*) the mediastinum and (*d*) the chest wall

Root or Main Bronchus Carcinomas —These cancers arise in the bronchial mucosa between the carina and the division of the bronchus into the main lobar bronchial branches Most often they appear as plaques in the bronchial mucosa which ulcerate and infiltrate the peribronchial structures and enter the lymphatics The typical roentgenographic appearance is that of a moderately dense shadow located centrally in the region of the hilus and which gradually fades laterally It is associated with hilar and mediastinal opacities *i e* with regional metastases The lateral margins of the shadow are not sharply circumscribed (Fig 127) *At this stage the infiltrative process has not obstructed the main bronchus* and there is no evidence of atelectasis Pleural effusion and secondary infection of the lung are also absent Metastases to ribs or other bones may or may not be present As the neoplasm progresses and extends the entire bronchial wall becomes involved and stenosed obstruction occurs

and massive atelectasis of the lung appears This is characterized by a homogeneously dense shadow on one side of the lung field The picture may resemble a massive pleural effusion except that the opaque half of the chest is smaller than the normal hemithorax, the heart and trachea are deviated to the involved side and the rib spaces are narrowed Because of the marked opacity of the involved side, the diaphragm usually cannot be visualized If infection occurs behind the obstruction

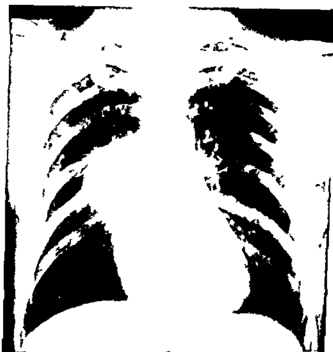


Fig 127 —Squamous cell carcinoma of the right main bronchus Note hilar density with infiltrating peripheral margins and absence of atelectasis

pneumonia abscess and irregular excavations may occur These various complications should be sought in all cases of massive atelectasis with a

or (*b*) excavations within the collapsed lung field suggesting a parenchymal breakdown behind the bronchial obstruction

Neoplastic extension to the pleura often results in pleural effusion which may further complicate the x ray picture The steadily accumulating pleural effusion soon compensates for the atelectasis

Occasionally the main bronchus tumor is more fungating than infiltra

tive In such instances massive atelectasis may occur early in the course of the disease before an infiltrative or hilar mass is apparent Differentiation from a nonmalignant obstructive lesion such as intraluminal bronchial adenoma cannot then be made

Bronchial Carcinoma Arising in Large to Medium Size Bronchi—This type of cancer also tends to be infiltrating but perhaps to a lesser degree than the preceding type It possesses a greater tendency to remain within the bronchial lumen for a longer time forming a fungating growth Atelectasis appears comparatively early and involves either a lobe or a large sublobar segment Here too a massive density is present at the site of the primary tumor and there occurs a rapid invasion of the hilar and the mediastinal lymph nodes characterized by linear densities extending medially to the enlarged hilar and mediastinal shadows Progress of the lesion follows the usual pattern Lymphatic dissemination along the peribronchial lymphatics to the pleura is common resulting in nodular densities and pleural effusion The neoplasm may also grow toward the hilus along the bronchial wall ultimately obstructing the main bronchus and causing atelectasis of the entire lung

In a number of instances the infiltrative neoplasm does not obstruct the bronchus but merely extends peripherally throughout the parenchyma of the entire lobe or segment in which the bronchus arborizes Atelectasis is then absent and the tumor appears on the films as a moderately dense patchy infiltration of segmental distribution Differentiation from a pneumonic infiltration on the basis of the pulmonary appearance alone may then be virtually impossible in which case evidence of metastases to the hilus the mediastinum or the bones may establish the neoplastic nature of the process Secondary infection in the lobe distal to the area of bronchial involvement is not uncommon and the appearance of pneumonitis and excavations in the involved lobes may overshadow the neoplastic densities giving the erroneous impression of a primary inflammatory process rather than a neoplastic lesion

Carcinoma Arising in Small Bronchi—This type of neoplasm is somewhat less infiltrating than the one described above It tends to be restricted to one area in so far as the radiographic appearance is concerned Since it arises in a smaller bronchus it is of necessity located at the periphery of the lobe near the pleura and its typical appearance radiographically is of a rather localized densely opaque area This density is quite well circumscribed but its margins may be only roughly delineated Since the involved bronchus is quasi terminal only fine short radiating strands of streak atelectasis may be observed and the visualized density represents the tumor itself

There are three common locations for these peripheral neoplasms

1 Along the lateral margin of the lung field where they may be seen as a localized lobular parabolic or triangular density based at the pleura

become permeated with cancer the walls of the bronchi and the blood vessels become thickened and are seen as streak like linear shadows radiating outward from the hilar zones In diffuse lymphangitic carcinosis these linear densities fan out into the lung fields from prominent hili Adjacent to the radiating lines are a large number of fine nodular densities which give the lung field a faint stippled overlay These densities are due to metastatic nodules at numerous points along the lymph channels The lymphatic spread not infrequently extends to the pleura resulting in extensive veining of the pleural surface with permeated lymphatic channels Localized nodules in the pleura may occasionally be visualized on the radiographs as scalloped thickenings of the marginal pleura Ultimately pleural effusion supervenes and obscures the entire lung field

Lymphatic metastases may also be local deriving from a carcinoma of a large bronchus and spreading along the lymphatics in only the involved segment Conversely a metastasis from a peripheral carcinoma may block the lymphatics and produce a retrograde extension from the tumor site along the lymphatics to the hilus The streaking and satellite mottlings are then similar to the generalized type of lymphangitic cancer but are seen only in a localized area Regardless of extent the lymphangitic linear densities usually extend to the hilar regions and involve the lymph nodes Prominence of the hilar shadows or actual discrete lymph node enlargements are thus commonly observed

(2) The hematogenous type of pulmonary metastasis is characterized by the presence of multiple rounded nodular densities irregularly scattered throughout the pulmonary parenchyma without patterned arrangement When there is wide dissemination the nodules tend to be more or less of uniform size When only few metastases are present the densities may vary considerably in size and range from 5 mm to several

tases may excavate and appear as multiple thin walled cavities Rarely calcification may be found within the nodules

(3) The combined type of metastasis occurs in the later stages of the neoplastic dissemination Either type may predominate or both forms may be equally prominent

It is important to point out that the above descriptions characterize the commonly observed metastases they do not include the many possible radiographic variations

DIFFERENTIAL DIAGNOSIS

The basic features utilized in the differentiation of malignant disease from benign or inflammatory diseases are (1) the density of the mass

and extending into the parenchyma for a variable distance The neoplasm often invades the adjacent segment of the rib by contiguity Indeed, the finding of a peripherally located, circumscribed homogeneous density with somewhat hazy borders overlying a destroyed rib is strongly suggestive of this neoplasm

2 At the apex of the lung (so called superior pulmonary sulcus tumor) In this cancer the pulmonary apex is homogeneously opacified There often occurs invasion and destruction of the upper ribs, the transverse processes, and the lateral aspects of the bodies of the adjacent thoracic vertebrae

3 Along the medial aspect of the upper lung field adjacent to the superior mediastinum, either anteriorly or posteriorly Here, the film reveals an irregular widening of the mediastinum, either to the right or to the left The pulmonary margin of the widened mediastinum is irregular, hazy, and tends to merge with the adjacent parenchyma The broadening of the mediastinum extends down to the homolateral hilus, which may show distinct lymph node enlargement The apparent widening and blurring of the border of the mediastium is due to the neoplastic involvement of the marginal lung, with invasion of the adjacent mediastinal pleura and fusion with the mediastinum Spread to the hilus occurs here as well as in the other forms, and enlargement of the hilar nodes is common

Terminal Bronchiolar Carcinoma.—This tumor has been widely known as "alveolar-cell cancer" At present, the term "terminal bronchiolar carcinoma" has been adopted Details concerning this type of cancer are outlined in Chapter 1

Radiologically, the neoplasm, when first observed, reveals homogeneously dense and irregularly shaped nodulations, the extent of which depends on the phase of the disease In the early phases there may be but a few, but in the more advanced phases the nodulations are multiple and almost evenly distributed throughout one or both lungs At still later stages, the isolated nodules coalesce forming a uniformly dense mass The film may also reveal a combination of a massive growth associated with the angular nodulations mentioned above A similar picture may also be provided by a cancer which, having arisen in an abdominal viscus, has metastasized to the lungs (See Chapter 1) Clinicians and radiologists should be aware of this possibility

METASTATIC NEOPLASMS IN THE LUNGS

These occur commonly in several forms (1) lymphangitic, (2) hematogenous, (3) combined

(1) The lymphangitic metastases usually involve the lymphatics in the bronchial walls and about the pulmonary vessels As the lymphatics

become permeated with cancer the walls of the bronchi and the blood vessels become thickened and are seen as streak like linear shadows radiating outward from the hilar zones In diffuse lymphangitic carcinosis these linear densities fan out into the lung fields from prominent hili Adjacent to the radiating lines are a large number of fine nodular densities which give the lung field a faint stippled overlay These densities are due to metastatic nodules at numerous points along the lymph channels The lymphatic spread not infrequently extends to the pleura resulting in extensive veining of the pleural surface with permeated lymphatic channels Localized nodules in the pleura may occasionally be visualized on the radiographs as scalloped thickenings of the marginal pleura Ultimately pleural effusion supervenes and obscures the entire lung field

Lymphatic metastases may also be local deriving from a carcinoma of a large bronchus and spreading along the lymphatics in only the involved segment Conversely a metastasis from a peripheral carcinoma may block the lymphatics and produce a retrograde extension from the tumor site along the lymphatics to the hilus The streaking and satellite mottlings are then similar to the generalized type of lymphangitic cancer but are seen only in a localized area Regardless of extent the lymphangitic linear densities usually extend to the hilar regions and involve the lymph nodes Prominence of the hilar shadows or actual discrete lymph node enlargements are thus commonly observed

(2) The hematogenous type of pulmonary metastasis is characterized by the presence of multiple rounded nodular densities irregularly scattered throughout the pulmonary parenchyma without patterned arrangement When there is wide dissemination the nodules tend to be more or less of uniform size When only few metastases are present the [illegible]

size than carcinomatous deposits Infrequently the nodular metastases may excavate and appear as multiple thin walled cavities Rarely calcification may be found within the nodules

(3) The combined type of metastasis occurs in the later stages of the neoplastic dissemination Either type may predominate or both forms may be equally prominent

It is important to point out that the above descriptions characterize the commonly observed metastases they do not include the many possible radiographic variations

DIFFERENTIAL DIAGNOSIS

The basic features utilized in the differentiation of malignant disease from benign or inflammatory diseases are (1) the density of the mass

(2) the margins of the mass, and (3) local invasiveness and metastases

Radiographic evidence of a circumscribed density, as differentiated from patchy, moderately opaque inflammatory infiltrations, may be seen on the routine films On the other hand, the mass (i e, the neoplasm) may be partially concealed within areas of secondary infection and require special studies, such as Bucky or tomographic examinations In general, the benign and malignant primary tumors are single masses, while the inflammatory lesions are multiple, patchy, less dense, and less



Fig 128—Irregular patchy infiltration of the right middle lobe in the region of the cardiophrenic angle

discrete ... dia tions whic ... n is suggested, even if the mass is small and its margins ... rply delineated, definite differentiation between benign and malignant disease cannot be made, since a small parenchymal carcinoma often shows well defined borders for considerable periods of time However, as such carcinomas grow larger, their margins become more lobulated and less sharply defined Large, single, round pulmonary densities with smooth borders are often benign tumors or cysts, particularly if they occur in or near the mediastinum It is thus clear that location, size, shape, density,

and margins of solitary parenchymal lesions play a role in distinguishing among them Each of these attributes must therefore be demonstrated radiographically

Endobronchial obstruction itself is of no great value in differential diagnosis Like carcinomas, benign tumors and inflammatory processes are capable of causing partial or complete obstruction In the majority of cases with extensive atelectasis, the lesion may be seen bronchoscopically and a biopsy taken However, the site of closure is frequently



Fig 129 —Bronchography showing irregularity, narrowing and foci of obstruction in branches of the right middle lobe

peripheral and hence cannot be visualized through the bronchoscope In such instances, tomography and bronchography may furnish valuable evidence Inflammatory occlusions often involve numerous branch

A sharp cut off is observed, at which point the contrast material may

demonstrate the smooth, convex surface of the adenoma as it bulges into the lumen and occludes it On the other hand, obstruction by a carcinoma tends to be locally irregular and constricting, since the tumor involves the entire circumference of the wall The bronchial lumen may be somewhat narrowed for a short distance proximal to the zone of complete closure Occasionally a fungating intraluminal carcinoma may give an *appearance similar to that of an adenoma*

Serial examinations, when available, are often helpful in the differential diagnosis of neoplastic and inflammatory diseases The rapid regression *which inflammatory lesions frequently undergo* is usually sufficiently characteristic to establish the non neoplastic character of the process However, rapid progression of the infiltration is much less helpful, since the inflammatory complications of neoplasms also may progress quickly

The presence of calcium in a solitary pulmonary density is of considerable *diagnostic significance When present,* it usually establishes the diagnosis of an infectious process (tuberculoma, histoplasmosis, and so forth) or a benign tumor (hamartoma). Primary carcinoma of the lung probably never contains radiographically visible *calcification Tomography* is usually the best procedure for the detection of calcification If a tomogram cannot be made, Bucky studies may be used with good results

Cavity formation within the infiltration is of much less diagnostic significance Marked irregularity and undulation of the cavitary walls suggest a malignant neoplasm, but such criteria should be accepted with reservation

The most convincing evidence in the differentiation between inflamma*tory, benign, and malignant disease is the demonstration of* metastases When found, they establish the nature of the process, and in addition preclude a radical intervention The search for metastases is mandatory *in all cases of malignant disease*

RADIOGRAPHIC DETERMINATION OF OPERABILITY

The criteria for operability of pulmonary cancer are given in some detail by Drs Burford and Ferguson (see Chapter 11) Generally pulmonary cancers may be classified into (1) inoperable, (2) operable, and (3) doubtfully operable

The radiographic methods utilized in demonstrating skeletal metastases, the involvement of the chest wall, or the opposite lung usually are the routine Bucky and chest films employed in general radiologic practice

The Mediastinum —The mediastinum, which is invaded most frequently by pulmonary carcinoma and whose status is of vital importance in establishing operability, is usually far less well explored than the lung, primarily because *the entire region is of homogeneous water density* on the chest roentgenograms The poorly delineated tracheal radiolucency

and the superimposed increased density of the thoracic spine further obscure the mediastinal structures. As a result evidence of mediastinal invasion on the frontal view is restricted to lateral and oblique views to the presence of densities in the hilar and mediastinal regions. A number of tests are required to study the various portions of the mediastinum which may be involved by metastasis.

Radiographic investigation of the mediastinum to determine operability in cases of pulmonary carcinoma includes the following procedures:

1 Fluoroscopy of the chest and larynx

2 Routine frontal, lateral and oblique views

3 Bucky studies of the thorax and the chest

4 Fluoroscopic and radiographic examinations of the barium opacified esophagus

5 Body section radiography of the chest

6 Thoracic angiography and angiocardiography (*a*) by injection of the arm vein to visualize the innominate veins, the superior vena cava and the pulmonary artery and its right and left intramediastinal branches, and (*b*) by injection into the medullary cavity of a rib in order to visualize the azygous venous system on the right side and the hemiazygous venous system on the left side.

Fluoroscopy.—In the detection of mediastinal metastasis fluoroscopy of the chest is used to find diaphragmatic paralysis. If both diaphragms move poorly during forced respiration, good motion on the normal side may be obtained by having the patient sniff or cough. Paralysis of a hemidiaphragm indicates phrenic nerve destruction and invasion of the middle mediastinum. During the fluoroscopy too, lateral local bulging of the mediastinum is looked for. However, the latter is better demonstrated on the films. During the fluoroscopy also the larynx is visualized as the patient phonates the letter "e." Fluoroscopy of the larynx is particularly warranted for patients with complaints of recent hoarseness.

Routine frontal, lateral and oblique views are, of course, a basic necessity in the study.

Bucky Studies.—Bucky studies of the thorax and chest are employed to obtain information concerning the dorsal spine and the medial aspects of the ribs. Evidence of invasion or destruction of these bones establishes at once the status of inoperability. These studies also demonstrate the trachea and the main bronchi better than the routine roentgenograms, but not as well as body section roentgenography.

Fluoroscopic and radiographic examinations of the barium opacified esophagus are essentials of mediastinal study. The thoracic esophagus in its descent lies intimately associated with the posterior aspects of the aortic arch, the trachea, the interbronchial area just below the tracheal bifurcation and the left auricle. The interbronchial zone is situated near both hilar regions and is one of the most common sites of lymph node

metastases The adjacent opacified esophagus is thus an excellent indicator of metastasis to this region *Lymph node enlargements or* ... mediastinal ...
may simply ...
invade its w... *... latter being shown* by mucosal pattern changes or fistulous tract formation The width of the space between the trachea



Fig 130—Carcinoma of the lung with extensive metastases and enlargement of the lymph nodes in the interbronchial area causing local narrowing and displacement of esophageal segment

and the barium filled esophagus is also routinely noted since paratracheal nodal enlargements may cause local widening The finding of wall invasion or fistulous tract formation indicates an inoperable status of the pulmonary carcinoma Simple displacement and extrinsic compression of the esophagus by adjacent nodes are not of themselves indicators of inoperability Such nodes may be surgically resectable even though the final prognosis be exceedingly poor In an occasional case the enlargement of the lymph nodes is inflammatory rather than neoplastic in nature and metastasis actually may be absent

Tomography—Body section roentgenography is a necessary feature of the mediastinal survey Special films at two to two and one half times the exposure employed for routine chest tomography are made at the 8 9 and 10-cm levels to visualize the mediastinum These films give a clear demonstration of the air filled radiolucent trachea and main bronchi in this region Enlargements of the paratracheal tracheobronchial and

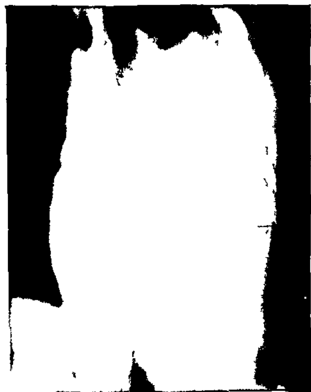


Fig 131—Squamous-cell carcinoma Body section roentgenogram demonstrating complete obstruction of the left main bronchus within the mediastinum less than 2 cm from the carina

interbronchial lymph nodes can be demonstrated by pressure and indentations thereon With extensive interbronchial deposits the interbronchial angle becomes widened Again although simple pressure or narrowing does not indicate absolute inoperability invasion of the wall and extension of the tumor into the lumen of the trachea or main bronchi does The site of involvement must be carefully evaluated in order to be certain that it is indeed within the mediastinum The entire

metastases The adjacent opacified esophagus is thus an excellent indicator of metastasis to this region Lymph node enlargements

the latter being shown by mucosal pattern changes or fistulous tract formation The width of the space between the trachea



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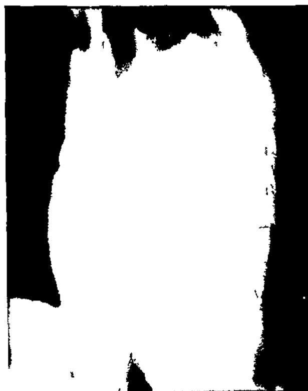


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trachea lies within the mediastinum but only the proximal 1.5 to 2 cm of the main bronchi are intramediastinal (Fig. 131). Pressure on, or invasion of, the main bronchi distal to this location occurs in the hilus outside the mediastinum and does not represent a categorically inoperable status.

Body section roentgenography is also of great aid in demonstrating direct extension into the mediastinum in cases of juxtahilar medial or paramediastinal parenchymal tumors. In such instances the neoplastic



Fig. 132.—Body section roentgenogram showing contiguous invasion of the mediastinum from a squamous cell carcinoma of the right upper lobe.

opacity is seen to extend from the lung field into the mediastinum and to fuse to form one homogeneous density encompassing the local pulmonary and mediastinal shadows on the proper tomographic level (Fig. 132). This finding has always indicated extensive invasion of the mediastinum by contiguity. It has therefore become one of the most important signs of inoperability in cases of medial pulmonary carcinomas. In analyzing the tomograms it is essential to be certain that the tumor xtends into the mediastinum. Cases of upper lobe massive atelectasis lso show paramediastinal opacity on the tomograms but this opacity epresents a collapsed lung and not the neoplasm. The usual findings f massive atelectasis assist in the differentiation of the two conditions.

Angiography—Thoracic angiography and angiocardiography has become a necessary and almost routine component of the mediastinal study It is performed by the rapid injection of 50 ml of one of the iodinated contrast materials into the antecubital vein on the side of the neoplasm Pictures are taken at 1 second intervals for about 20 seconds with a serialographic change device Primary interest concerns the major vessels of the mediastinum rather than the heart These vessels comprise the innominate vein the superior vena cava and the pulmonary artery and its branches within the mediastinum It is desirable to visualize all of these

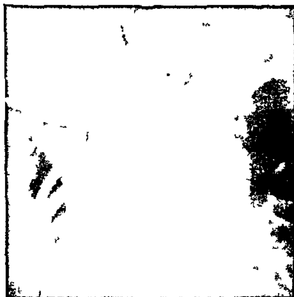


Fig 133—Mediastinal invasion from a squamous cell carcinoma in the right upper lobe Thoracic angiogram showing narrowing, partial obstruction and mottled intraluminal defects in a segment of the superior vena cava Note satisfactory filling of the vessel on either side of the narrowed section There is a marked collateralization

vessels They lie in different parts of the mediastinum and the various areas may thereby be explored for metastases The opacified vessels may show simple displacement or smooth narrowing with semilunar indentations due to extrinsic pressure from adjacent enlarged nodes Such nodes are theoretically resectable and these findings do not indicate categorically inoperability Complete obstruction of a vessel on the other hand has always been found associated with inoperable metastases to the mediastinum and is presently considered as indicating a definitely inoperable cancer If the obstruction is venous extensive collateral circu

lation is always observed Obstructions of the pulmonary artery or its right and left branches within the mediastinum are not accompanied by a collateral circulation Only abrupt cessation of filling is observed at the occlusion site within the mediastinum whereas the remaining vessels fill normally The remaining type of positive finding is the appearance of a segment of an opacified vessel with normal filling of the vessel on each side of the involved segment Some narrowing of the abnormal section is usually present as well This appearance has been found almost exclusively in the veins (Fig 133) It is due to invasion



Fig 134—Visualization of the azygos vein system by injection of the vein (Normal azygogram)

of the wall of the vein from the adjacent mediastinum and always indicates an inoperable lesion

Significant involvement of the posterior mediastinum may be shown by demonstrating displacement alteration or obstruction in the azygos or hemiazygos veins which lie in this region Visualization of the azygos vein on the right side or the hemiazygos vein on the left side is obtained by placing a narrow aspiration needle into the cancellous center of one of the lower ribs posteriorly Ten to 15 ml of iodinated contrast material is injected as rapidly as possible and a film is made just at the conclusion

of the injection About 5 to 10 seconds are required for injection at the end of which period much of the contrast material has left the cancellous space, has opacified the intercostal veins and entered and outlined the *azygos vein up to the superior vena cava (Fig 134) In cases of obstruction* the opacification of the azygos ceases abruptly well below the level



Fig 135 —Invasion of the mediastinum from carcinoma of the esophagus There is destruction of the azygos and hemiazygos veins Note the downward flow of the contrast material into the ascending lumbar veins

of the superior vena cava and there is a retrograde flow of contrast material down the azygos vein into the ascending lumbar vein and into the inferior vena cava (Fig 134) Other collateral channels lead to the superficial veins of the thorax the costoaxillary and lateral thoracic veins thence to the axillary veins and finally into the superior vena cava Obstruction of the azygos vein makes the cancer inoperable

Chapter 10

Pulmonary Function*

Roger H L Wilson, M D , and Seymour M Farber M D

The pulmonary physiologist is another specialist who can contribute to the management of patients with tumors involving the lungs His function is to help interpret and correlate the alterations in cardiopulmonary function based on pathological changes caused by tumor in the lung

In neoplastic disease the problem of spread or recurrence becomes the focus of attention Neoplasms involving the lungs may produce major effects upon pulmonary function which in turn can cause discomfort and disability to the patient and eventually may be the chief factor in death It is essential moreover, to consider the adequacy of pulmonary function in deciding on certain modalities† of therapy, *e g* pneumonectomy versus lobectomy In many cases it is necessary to consider not only the tumor itself and its effects upon lung function but also the fact that many patients fall into an age group in which obstructive emphysema is common In this group of patients the effects of the tumor may be even more serious than in patients with relatively normal lung function In patients with a pulmonary neoplasm therefore evaluation of the functional state is required in addition to the usual diagnostic work up proof of tumor and judgment of operability

GENERAL PRINCIPLES OF PULMONARY FUNCTION

The lungs are a system of balloons blown up by atmospheric pressure to occupy a space in the thorax They are ventilated by rhythmic alterations of the thoracic volume and are perfused by the output of the right heart A delicate membrane (Beischer) separates the capillary from the alveolus allowing relatively free transport of oxygen and carbon dioxide between avleolar gas and capillary blood Under normal circumstances

* [illegible] University of [illegible] e National Institutes of Health U S Public Hea[illegible]

†In tumor the effect of therapy on function may require study *e g* the effect of radiation on lung function

ventilation will increase to accommodate almost any bodily need Likewise the distensibility of the normal pulmonary vascular bed permits a considerable rise in cardiac output without development of pulmonary hypertension Impairment of elastic recoil of bronchial patency of anatomical vascular bed and finally impaired rib cage or diaphragm movement may produce profound alterations in the efficiency of this system To understand the effects of disease upon pulmonary function it is best to consider some of the factors separately

Ventilation—The normal person at rest breathes approximately 3 to 5 liters per minute per square meter of body surface This varies with age and sex The resting level may increase fortyfold for short periods of time For this rise to occur normal pulmonary recoil patent bronchi a thin pleura and a normally functioning chest wall and diaphragm must be present These purely mechanical factors may be seriously disturbed in the presence of disease

One of the most common disturbances is that of the bronchial patency *The bronchi are musculo-elastic structures becoming exceedingly narrow* at their final ramifications A significant factor in the maintenance of bronchial lumen is the elasticity of the structures around them Localized obstructive emphysema seen with certain tumors and foreign bodies occurs when the tumor is of such a size that the bronchus is blocked in expiration only Generalized obstructive emphysema may occur if the elasticity of the interbronchial tissue is destroyed This phenomenon gives rise to a serious mechanical defect in ventilation In this situation an overinflation of the lung may occur Narrowing of large cartilaginous bronchi will impair both inspiration and expiration Since only the membranous posterior wall of the trachea and the intercartilaginous portions of bronchi are affected by the pressure gradient the effect will be not so much to produce emphysema as to slow the flow of air producing a mechanical resistance to both phases of ventilation

The mechanical disturbance in early pleural effusion is a result of relaxing of the lung later pleural thickening acts by stiffening the mechanism of the lung

The presence of diaphragmatic paralysis destroys the ability of the thorax to enlarge fully in inspiration since movement of the paralytic diaphragm is in the direction opposite to that of the normal diaphragm

However ventilation cannot be considered purely as volume per minute or per breath *Alveolar ventilation* must be considered since it is that part of a breath actually used in gas exchange The useful volume of a breath is the difference between the total volume of gas and that making up the respiratory dead space (Bohr) This consists both of a relatively fixed anatomic volume of the trachea and bronchi and an additional entity (called the series dead space) The latter is defined as areas of lung ventilated but not perfused Inadequate ventilation of perfused alveoli may also exist and accounts for much of the arterial anoxia in emphysema

patients and those with lung tumor. Inadequate alveolar ventilation may result from any anatomic alteration of lung parenchyma, and particularly from bronchial obstruction

Ventilation is primarily under control of the respiratory center in the medulla, the cells of which are sensitive to change of carbon dioxide tension and pH. The solubility and rapid diffusion of CO_2 is such that alveolar CO_2 tension is usually not more than 3 mm Hg below the arterial level and hence, for practical purposes, is accepted as equal to it. The CO_2 tension in the capillaries of the medulla has not been measured, yet it is such that the normal arterial and alveolar CO_2 tensions are held at approximately 40 mm of mercury. This may be modified by alteration of blood flow within the medulla, as in arteriosclerosis of the basilar and posteroinferior cerebellar arteries and their branches, producing hyperpnea and fall of arterial CO_2 tension. Increased medullary blood flow will alter the arterial CO_2 tension in the opposite direction and produce an apparent change in the baseline sensitivity of the center. However, the respiratory center may in fact alter the baseline sensitivity.

There are chemoreceptors in the great vessels sensitive to lowered arterial oxygen tension, thus, hypoxia will produce stimulation of respiration independently of the CO_2-sensitive medullary center. These chemoreceptors constitute a secondary mechanism. They are operative only under circumstances such as altitude adaptation, extreme effort in the normal state, and clinically in the presence of severe hypoxia, especially if the center is depressed. Such failure is seen most characteristically in the accumulation of carbon dioxide with hypoxia associated with emphysema, and in anesthesia and allied states. Reflex mechanisms in the lungs and chest wall, such as the Hering Breuer and intercostal reflexes also control the depth of ventilation. The precise interaction of medullary blood flow, hypoxia, and reflex factors is still obscure.

Perfusion.—Much of what has been said about ventilation is true of perfusion. The normal output at rest of the right heart ranges from 4 to 5 liters per minute. An increase to about 3 times this value is possible if needed. Since oxygen is not fully extracted from capillary blood when the body is at rest, the potential oxygen supply to the tissue is far greater than necessary. The pulmonary arterial bed is extremely capacious and can accommodate considerable increments of volume flow without a rise of pressure. If the arterial bed is restricted, a rise of pulmonary artery pressure will occur when an increase in cardiac output is required. With further restriction, pulmonary hypertension develops at rest with hypertrophy of the right ventricle. Eventually the output of the heart can be maintained only at such high pulmonary arterial pressure that the right ventricle will fail. Restriction of flow may occur through a variety of mechanisms, including thromboembolic disease, pulmonary arterial sclerosis, the closing off of the vascular bed associated

with failure of ventilation of alveoli (Berggren) as a result of precapillary anatomosis with an enlarged bronchial circulation and lastly with alve olar destruction

As with ventilation perfusion cannot be considered only in terms of restriction of total output Deviation of blood through unventilated areas or other channels by which venous blood (i e blood which passes through the lung unchanged) becomes admixed with arterial must also be evaluated In normal lungs such deviation is not extensive but in the presence of pulmonary fibrosis emphysema and certain other con ditions it becomes prominent Then the effectiveness of an already restricted cardiac output becomes further lessened by an increase in the percentage of venous admixture

A brief note may be added concerning the bronchial circulation The bronchial venous circulation normally drains directly into pulmo nary veins Under certain conditions particularly associated with inflam matory disease and in some neoplastic disease the bronchial artery circulation forms a precapillary anastomosis and considerable amounts of already arterialized blood pass through the pulmonary capillaries (Liebow) This increases the pressure in the pulmonary arterial bed and results in diminution of the pulmonary artery flow Also this recir culation produces a disparity in the output of the two sides of the heart and may give rise to increased work for the left ventricle This flow is somewhat difficult to study physiologically although work of clinical importance has been done by Bing and Nakamura

The Membrane Component—The existence of a thin membrane be tween the pulmonary capillary and the alveolus has been shown by Beischer Normally this membrane is thin enough to present little barrier if any to the diffusion of gases across it and particularly to carbon dioxide Oxygen on the other hand is considerably less diffusible and any thickening of the pulmonary alveolar membrane will lead to some decrease of oxygen tension in pulmonary capillary blood without altering significantly the diffusion of CO Such a condition is referred to as alveolar capillary block (Austrian) It occurs much less commonly than disturbances of gas exchange due to bronchial destruction and emphy sema It may be one of the major causes of dysfunction in beryllium granuloma of the lung, sarcoidosis or in lymphatic spread of carcinoma

Conclusions—Pulmonary disability essentially is a combination of fac tors In studying the effects of any disease process on pulmonary function no single facet should be taken exclusively It is necessary to have some knowledge of both effective alveolar ventilation and gas exchange The pulmonary vascular bed may be augmented or restricted Most commonly it is restricted in disease in which case as a converse of the ventilation problem the perfusion of unventilated alveoli is important The mem

brane component emphasizes the distinction between carbon dioxide elimination and oxygen consumption.

These factors must be considered not only with the patient at rest but also with the patient at some activity, since an increase of ventilation and perfusion may be necessary to support the latter. Also, there may be an increased effort in breathing, which may augment oxygen need and CO_2 production considerably (Bader) From an understanding of these factors one may plan therapy for both the neoplastic disease and the associated pulmonary dysfunction, through which the discomfort of shortness of breath may be materially alleviated

THE EFFECTS OF THE TUMOR IN RELATION TO SITE

The site of the tumor and its size will be of major importance in determining its effect on pulmonary function

Intrabronchial Tumors.—The majority of intrabronchial tumors produce their first effect by causing bronchial obstruction Early, the obstruction may cause at least transiently localized emphysema distal to the obstruction, later, atelectasis and infection of the area will occur When the tumor is in a main lobar bronchus, ventilation will cease and perfusion will be much reduced Obstruction to a whole lung will give rise to great disability, particularly if there is preexisting emphysema, which is common in patients with bronchiogenic carcinoma Patients with a considerable degree of obstruction due to tumor may not be particularly hypoxic because of the shunting of blood from the side of the tumor to the "normal" lung Carbon dioxide retention is likely to be remarkable only in a patient with coexisting emphysema When the atelectasis is present for an extended time, some overdistension of the rest of the lung may occur This may materially diminish pulmonary function from the point of view of the unaffected area, since overdistension can aggravate the impaired mechanical function of an already emphysematous lung

It has been observed that very many patients with bronchiogenic carcinoma complain of increasing dyspnea After resection the dyspnea may be relieved For this reason, when dyspnea and tachypnea disproportionate to the other findings occur, the cause is generally an extensive obstructive lesion, composed of tumor with infection and collapse of the pulmonary parenchyma distal to it

Parabronchial Tumors.—Parabronchial and paratracheal tumor masses tend to impinge upon tracheobronchial patency This is seen in those primary bronchiogenic tumors in which an "ice berg" effect develops, with a large mass of tumor impinging on a major bronchus from the outside It also occurs in mediastinal lymphadenopathy and large mediastinal tumors The effects are more obvious in infiltrative tumors such as

carcinoma and teratoma than in benign tumors lymphomas and dermoids because of fixation as well as narrowing of the air passages Such impingement causes some degree of stridor which although difficult to appreciate clinically may readily be seen on appropriate study The impedance occurs in inspiration as well as expiration and maximal ventilation may be markedly diminished Moreover the very position of these parabronchial tumors may obstruct the blood supply from the pulmonary artery Pulmonary vein drainage and the venous drainage from the upper part of the body also may be impaired Added to the increased work of breathing due to narrowing of major air passages there then may be a tendency toward fluid accumulation in the lung which will stiffen it render ventilation uneven and give rise to alveolar capillary block Thus disability from parabronchial tumors may be more extensive than is commonly realized

Peripheral Solid Lesions.—These may be primary or metastatic By definition they are those tumors not producing a recognizable bronchial obstruction Physiologically their effects are commonly not very great In *hemangioma of the lung considerable venous admixture—sufficient*

Disseminated Tumors.—It is in lymphangitis carcinomatosa that perhaps the greatest degree of pulmonary insufficiency is found In this condition a number of factors are present The lesions are widely disseminated throughout the lung involving as a rule not only the peribronchial structures but the membranes as well The development of lymphangitis carcinomatosa was observed in a patient with previously diagnosed pulmonary emphysema who was formerly seriously acidotic and quite hypoxic The hypoxia deepened and the respiratory acidosis became ameliorated due to alveolar capillary block The degree of cor pulmonale markedly increased due to tumor obstruction of pulmonary circulation In such patients alveolar ventilation decreased perfusion and increased venous admixture as well as diffusion difficulty are involved in producing a rapidly increasing disability which terminates in cardiopulmonary failure In multiple hematogenous metastatic disease the disability is much less severe as a rule the main effects being an alveolar loss and increased stiffness of the lung By study of these factors some differentiation may be made between the two conditions

Pleural Lesions.—Both in mesothelioma of the pleura and in the spread of malignant neoplasms beyond the pleural barrier pleural effusion with rapid fibrin deposition is common Some pulmonary deflation will occur being uneven and most marked in the subpleural zone The lung will be relatively fixed As a result a considerable loss of useful alveoli and unevenness of ventilation occurs The vascular disturbance is secondary to the ventilatory and will not in itself be sufficient to reduce the pulmo-

nary capillary bed to the extent of producing pulmonary hypertension. Usually hypoxia is not very marked. These lesions may therefore produce definite physiological effects clinically manifested, as a rule, only by moderate dyspnea with exercise.

Miscellaneous Effects.—Interruption of the phrenic nerve is not uncommon in late neoplasia and produces an increased disability. This is most common in posterior peripheral tumors of the lung, posterior mediastinal tumors and metastases in teratoma, and in the superior sulcus tumor. The problem is one of ventilatory loss. The diaphragm becomes paralyzed and may be very difficult to stabilize, since the use of pneumoperitoneum will merely cause it to rise and thus further reduce the lung volume on that side.

The loss of the left recurrent laryngeal nerve seen in cancer of the left lung is of indirect physiological importance, since the mechanism of cough may be markedly impeded. As a result, secretions accumulate on both sides causing further alveolar obliteration.

SPECIAL FACTORS IN RELATION TO THE TYPE OF TUMOR

Vascular Problems.—The vascular pattern may be of some importance in differentiating primary bronchiogenic from metastatic tumors. The blood supply of primary bronchial tumors is usually by the bronchial artery which becomes hypertrophied proportionately to the vascular supply of the tumor. Normally the bronchial artery drainage is through the pulmonary vein system and back to the left heart. The bronchial vein system drains into the systemic venous return to the right heart. The direction of the venous return from the tumor depends in part on the condition of the bronchial tree and is not necessarily uniform. In very highly vascular tumors the amount of blood flowing through the bronchial artery system into the tumor is apparently significant in relation to the cardiac output.

In metastatic tumors, on the other hand, the arterial supply is commonly from the pulmonary artery. In highly vascular tumors the amount of shunting in the pulmonary circuit may be extensive and will cause arterial hypoxia. The only primary tumor of the lung that behaves in the manner of metastatic tumors appears to be cavernous hemangioma, which may be very small and difficult to localize. Pulmonary angiography may be useful in this regard.

The presence of full arterial saturation does not necessarily suggest primary rather than metas ... or. Oxygen d ... however, particularly with a high c ... t usually indi ... tic dis ease. Oxygen desaturati ... n in metasta ... roma, thyroid carcinoma, and ch ... a but is not ... in less vascular metastases. Whe ... of these

possible resection may frequently be worthwhile physiologically if the extent of the disease is such as to make it a reasonable therapeutic effort

Reflex Problems —These are at once interesting yet poorly understood factors in pulmonary physiology The two known sets of pressure-sensitive receptors in the lung and in the skeletal muscle are involved in the cessation of inspiration permitting expiration to occur The respiratory center in the medulla initiates a further breath Pulmonary tumors both directly and indirectly may cause premature and increased numbers of impulses arriving at the medulla Under these circumstances tachypnea with dyspnea may be observed This not only is a disadvantageous way of ventilating but is also uncomfortable to the patient and may indicate the need for therapy In the case of infiltrative lesions there may be advantages in blocking the Hering Breuer reflex There is a possibility that a recently developed compound a conjugation of a local anesthetic with a glycol does this selectively It is currently undergoing laboratory evaluation

Ventilatory Restriction —Restriction of ventilation can occur in numerous ways in neoplastic disease involving the lung Where ventilatory restriction is on a reflex basis it may be amenable to chemotherapy However ventilatory restriction on a mechanical basis should also be treated The most serious consequences of ventilatory restriction are CO retention and hypoxia

THE EVALUATION OF PULMONARY FUNCTION IN RELATION TO THERAPY

Since tumors involving the lung may produce such a great effect on pulmonary function some form of objective study of this function is desirable especially since therapy of the tumor may considerably alter it for better or for worse Pulmonary function tests have been enormously elaborated in the past few years and time and experience are required to perform and to interpret them correctly Three separate types of pulmonary function tests are recognized

1 Simple tests requiring little equipment and little experience to interpret which may indicate to the clinician the major type of physiological disturbance and may often help him to evaluate it

2 Elaborate studies required only for patients in whom the nature of the disease as well as the best method of treatment presents a real difficulty

3 Research procedures designed to increase knowledge of physiological disorder

These three types of tests are frequently confused Moreover there is a tendency to seek objective numerical evidence of the condition irrespective of its clinical usefulness Any procedure must produce a

nary capillary bed to the extent of producing pulmonary hypertension. Usually hypoxia is not very marked. These lesions may therefore produce definite physiological effects, clinically manifested, as a rule, only by moderate dyspnea with exercise.

Miscellaneous Effects.—Interruption of the phrenic nerve is not uncommon in late neoplasia and produces an increased disability. This is most common in posterior peripheral tumors of the lung, posterior mediastinal tumors and metastases, in teratoma, and in the superior sulcus tumor. The problem is one of ventilatory loss. The diaphragm becomes paralyzed and may be very difficult to stabilize, since the use of pneumoperitoneum will merely cause it to rise and thus further reduce the lung volume on that side.

The loss of the left recurrent laryngeal nerve seen in cancer of the left lung is of indirect physiological importance, since the mechanism of cough may be markedly impeded. As a result, secretions accumulate on both sides causing further alveolar obliteration.

SPECIAL FACTORS IN RELATION TO THE TYPE OF TUMOR

Vascular Problems.—The vascular pattern may be of some importance in differentiating primary bronchiogenic from metastatic tumors. The blood supply of primary bronchial tumors is usually by the bronchial artery which becomes hypertrophied proportionately to the vascular supply of the tumor. Normally the bronchial artery drainage is through the pulmonary vein system and back to the left heart. The bronchial vein system drains into the systemic venous return to the right heart. The direction of the venous return from the tumor depends in part on the condition of the bronchial tree and is not necessarily uniform. In very highly vascular tumors the amount of blood flowing through the bronchial artery system into the tumor is apparently significant in relation to the cardiac output.

In metastatic tumors, on the other hand, the arterial supply is commonly from the pulmonary artery. In highly vascular tumors the amount of shunting in the pulmonary circuit may be extensive and will cause arterial hypoxia. The only primary tumor of the lung that behaves in the manner of metastatic tumors appears to be cavernous hemangioma which may be very small and difficult to localize. Pulmonary angiography may be useful in this regard.

The presence of full arterial saturation does not necessarily suggest primary rather than metastatic tumor. Oxygen desaturation, however, particularly with a high cardiac output, usually indicates metastatic disease. Oxygen desaturation is common in metastatic hypernephroma, thyroid carcinoma, and chorioepithelioma, but is not so common in less vascular metastases. Where the position of these tumors makes excision

of the volume ventilation of each lung and to this may be added fluoroscopic observations of unevenness of filling or emptying Attempts to do this with x ray kymography have often been exceedingly difficult to interpret although this method of examination deserves further study The use of inspiration expiration films for a rough estimation of the residual volume in the lungs at the end of expiration is of value This method does not give a precise figure yet it permits one to observe whether the residual volume appears normal moderately increased or markedly increased In radiological study of lung volume no deduction may be made as to the use of air drawn into either lung or any lung area since the study is merely one of volume change using the measurement of an area To study the alveolar ventilation differentially it is necessary to use techniques such as bronchospirometry which will be discussed later

Other simple studies include the use of the electrocardiogram and the hematocrit The venous pressure and the circulation may amplify these findings always remembering that a rise in venous pressure without a visible pulse wave is more likely to indicate a superior mediastinal obstruction syndrome than the presence of a tumor The value of electrocardiographic changes in the diagnosis of right ventricular hypertrophy is well known In the presence of marked arteriovenous shunting or of long continued hypoxia or both a rise in hematocrit is usually seen Where changes in the electrocardiogram suggest right ventricular hypertrophy and the hematocrit is elevated a diagnosis of cor pulmonale is justified This has a material effect upon the prognosis with major surgery since it is unlikely that the vascular bed of the lung will be increased and it may result in increased cardiac embarrassment In such an event it is necessary to evaluate the patient further before major surgery is undertaken

With these simple tests the majority of patients with pulmonary neoplasms may be evaluated for surgery or other types of therapy and the progress of a patient can be followed within the clinical need Exercise tests are variable according to a number of factors including the amount of activity to which the patient is accustomed Standardized exercise tests however are frequently used the most common being the Baldwin Cournand and Richards the Warring and the Gilson Hugh Jones tests None of these require complicated apparatus

More Exhaustive Study of the Patient —This becomes necessary

1 When the results of clinical and simple pulmonary function studies indicate doubt that the patient undergo surgery

2 In patients whose pulmonary function tests show a considerable degree of pulmonary function remaining but whose symptomatology is disproportionate

result commensurate with the effort of producing it The best method is to regard the study of pulmonary function in a patient as a consultation in which clinical understanding is increased by the use of relevant tests, rather than to perform a standard battery of studies As a result, there should be considerable variation in the type of study, depending upon the patient's disorder

Studies Possible in the Office or Outpatient Clinic with Minimally Trained Personnel.—Direct ventilatory studies are the simplest of all These include study of the timed inspiratory and expiratory vital capacity, recorded on a fast moving drum, and a qualitative study of the effects of CO_2 administration Using such readily available equipment as a basal metabolic-rate apparatus, in which the drum has been speeded up at least 10 times, one can record quite small changes of ventilatory function The resistance of the system should be reduced as much as possible by removing the soda lime canister and using wide tubing

The timed inspiratory capacity is not so often used as the timed expiratory capacity, and unfortunately, the timed expiratory capacity is usually meant when one refers to the timed vital capacity However, tumors may cause marked changes in the velocity of inspiration, and these are important to observe Normally one should be able to expell at least 50 per cent of the vital capacity in 1 second, and 95 per cent in 3 seconds The inspiratory velocity should be considerably greater, with total inspiration taking not more than 1½ seconds Deviation from this must be regarded as abnormal Such techniques are sensitive enough to reveal quite small changes Velocity changes generally are of greater importance than volume changes

Normal values for the vital capacity in relation to age and sex are given by the following formulas

Males —[27 63–(0 112 × age)] × height in cm
Females—[21 78–(0 101 × age)] × height in cm

From these, the expected timed inspiratory and expiratory vital capacity can be calculated The normal partitions of the vital capacity are (Baldwin *et al*)

Inspiratory reserve—1/2 (approximately)
Tidal volume —1/6
Expiratory reserve —1/4

Comparison of observed with expected figures in relation to available clinical information is often sufficient to decide if surgical excision is possible

This information can be amplified by the use of inspiration expiration posteroanterior chest *x*-rays together with fluoroscopy Measuring the area change in each lung with a planimeter gives a rough approximation

When the elaborateness of the surgical team and the time discomfort and seriousness of the operation is measured against the advantages of bronchospirometers the use of bronchospirometry—even at its most complex—does not appear so formidable

Thus far our attention has been directed chiefly at the direct study of one lung against the other from the point of view of surgical excision Many other pulmonary function tests are largely concerned with the function of the lungs as a whole and their use may be extended as well to patients who are not candidates for surgery They may also be used for isolated disease in a relatively normal lung to define the nature of the abnormality of function and they are of some aid in assessing disability due to mediastinal tumor

Studies of residual volume and intrapulmonary mixing require a relatively simple apparatus that can be used in almost any hospital * With such an apparatus the presence of localized obstructive emphysema in a normal lung can be confirmed the changes typical of generalized emphysema can be found although these would probably have been already diagnosed by spirogram Limits of oxygen uptake on effort may be determined The design of the apparatus is such that bronchospirometry may be done in addition to other ventilatory studies

Such studies may be amplified by combined blood gas studies in which the equilibration of blood in the lung is indirectly estimated Blood gas studies are somewhat elaborate requiring particularly expert technical assistance As a rule a large collecting recording spirometer is needed to study expired air and arterial samples under various conditions of breathing and exertion This type of study is designed to relate ventilation and perfusion it permits evaluation of such factors as the anatomic and series dead spaces the diffusion capacity of the lung for oxygen the venous admixture and the alveolar arterial capillary pressure gradients (Comroe Riley Donald and their associates)

A simple method of determining the degree of arterial oxygen unsaturation employs an absolute-reading oximeter (Wilson)

THE PHYSIOLOGICAL APPROACH TO THERAPY

Physiological study aims not only to define a given condition but to help direct therapy The more serious the disability the more intense should be this study

Place of Physiology in Surgery of Neoplastic Disease of the Lung— The importance of physiological approaches to surgery becomes greater when the patient is a poor risk although for extensive surgery any patient may need physiological assistance Intermittent positive pressure breath

*Such an apparatus is the Pulmotest Godart and Pulmo Analysor Godart distributed by Instrumentation Associates in New York

3 When there is doubt as to the nature of a serious physiological disturbance and therapy is planned

Perhaps the greatest attention has always been paid to the evaluation of a patient for major surgery This is more true with bronchiogenic carcinoma than with mediastinal tumors, since in the latter, little or no pulmonary embarrassment is likely to result from intervention In metastatic tumors local excision is usually all that is planned The physiologist is often asked if a given patient can tolerate a pneumonectomy When one lung is totally out of circuit because of an obstructing lesion what function if present will be the contribution of the other lung Dysfunction, on the other hand, can at least in part be laid to the atelectatic lung Under these circumstances no further study is required even if the pulmonary-function tests already done show a considerable impairment of pulmonary reserve If a patient in such circumstances can walk with comfort, he is a candidate for surgery and is likely to improve Naturally, from a physiological standpoint, such a patient must be very carefully watched throughout the operation and in the postoperative phase

A more difficult situation exists when only part of a lung is involved in the tumor The greater the amount of functioning lung tissue in the side where surgery is planned, the more important it becomes to assess the functional value of that lung This requires bronchospirometry isolating the lungs from each other using a wide double lumen catheter inserted into the left main-stem bronchus With the catheter in place volume ventilation, oxygen uptake, CO_2 production, mixing, and diffusion can be studied in either lung separately during both rest and exertion The combination of bronchospirometry with the study of blood materially increases the former's usefulness Arterial oxygen desaturation is better observed by direct measurement than with a simple oximeter Simultaneous use of an occlusive balloon tipped catheter in the pulmonary artery to the side of the tumor produces an acute "pneumonectomy" This may prove to be a most important advance in technique in analyzing the consequences of pulmonary artery ligature

Bronchospirometry (Birath *et al*) with or without the occlusive catheter in the affected pulmonary artery, enables the physician to study maximal oxygen uptake, ventilation, and vital capacity on the good side, independent lung residual volumes may also be determined To produce valid results with bronchospirometry requires adequate equipment, a trained team of experienced pulmonary physiologists, and continuous application, since small variations of technique may produce widely differing results This is not, therefore, a procedure for the average hospital but rather for centers in which there are enough cases to justify such an installation On the other hand, such a study should not be denied to a patient when serious doubt of operability exists

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ing with bronchodilators before surgery will reduce mucus retention to its minimum and thus make for an easier postoperative course. Breathing exercises should also be introduced at this time to accustom the patient to an important feature of his postoperative rehabilitation. Pre-anesthetic medication should be considered in relation to pulmonary function. During the actual operation the major problem is one of ventilation. This is particularly important in patients who already have severe respiratory dysfunction.

The anesthetic agent is usually associated with a closed circuit controlled respiration system in which the inspired O_2 is above normal atmospheric concentration. Under these circumstances there is an excess of O_2 in the alveoli and hypoventilation will not necessarily produce cyanosis although CO_2 may be retained. Acidosis during and after the surgery is a major cause of increased mortality and morbidity. As in metabolic acidosis respiratory acidosis may cause a change of potassium level which in turn can give rise to ventricular fibrillation or cardiac arrest. Difficulty in restarting the patient's own ventilation postoperatively will also occur when the acid base balance has been upset during the operation. Very few anesthetic apparatuses incorporate a ventilation meter giving the anesthetist actual values of the tidal volume. Hence he is by and large dependent upon his own observation by eye and by hand pressure or upon the setting of an automatic ventilator and these criteria are often insufficient to enable him to maintain normal body acid base balance. Surgery and anesthetic agents themselves may alter the normal condition. In order to study acid base balance it is essential to follow the arterial or alveolar CO_2 tension. The latter is best followed with a CO_2 meter of the infrared type. Almost as convenient however is the use of arterial samples and the estimation of pH and CO_2 content with subsequent calculation of the CO_2 tension. By this means one can correct ventilation to levels adequate for CO_2 excretion.

During surgery the pulmonary arterial pressure should be measured as mean pressure; if necessary a saline manometer can be used. If this is elevated or becomes elevated after ligation of the pulmonary artery then there are certain to be serious postoperative problems of ventilation and perfusion and the patient should be watched carefully. Difficulty may arise in transfusions if there has been a marked rise in pulmonary artery pressure since this may be followed by a rise in venous pressure and the development of cor pulmonale.

Another problem arising during surgery is whether or not to reduce the dead space in the operated hemithorax. Failure to do so will cause overdistention of the remaining lung which already may be emphysematous. This is perhaps most easily solved by doing a phrenic nerve interruption together with a pneumoperitoneum. The pneumoperitoneum should be maintained until sufficient fibrin has been laid down

on the elevated paralyzed diaphragm to stablize it Using this technique as much as half the space in the hemithorax may be taken up In addition some surgeons finish the operation with a "tailoring" thoracoplasty excising portions of the second and third ribs This does not produce an unstable chest wall in the early postoperative phase These procedures may be indicated more frequently in older patients undergoing pneumonectomy for carcinoma than we believe at present

In the immediate postoperative phase hypoventilation occurs after controlled respiration is stopped and before the patient recovers full consciousness During this period some form of assisted ventilation is desirable and is most easily achieved by using intermittent positive pressure equipment There is some controversy as to whether a tracheotomy is desirable it does make the application of intermittent positive pressure breathing easier since inflation of the stomach is less likely to occur than with a mask With the recovery of consciousness ineffective hypopnea and retained secretions are the two major difficulties At this point the introduction of breathing exercises becomes very helpful and such aids as intermittent positive pressure breathing with a broncho dilator and the use of a cough machine may materially improve the patient s condition Antibiotics are indicated preoperatively and post operatively

Over the long term, patients with some degree of cardio respiratory failure require treatment of the failure not only for maximum comfort but for prolonged life All the techniques normally used on a patient without a neoplasm are applicable to the patient with neoplasm even though he may have undergone more radical surgery These techniques include the use of antibiotics the use of ventilatory assistance such as intermittent positive pressure breathing the maintenance of a good bronchial toilet with the aid of intermittent positive-pressure devices and the use in some instances of corticoids to control secretions Both the surgeon and the physician should follow the patient s postoperative course Pulmonary function should be re evaluated by simple tests as soon as the patient is free of pain and his condition has become stabilized by so doing continued therapy can be planned

The same considerations that apply to bronchiogenic carcinoma apply also to mediastinal tumors except that no lung is likely to be excised However the pleural spaces may have been entered and ventilatory difficulties are as urgent In local resection of lung tumor it is necessary to use intermittent positive pressure cautiously in maintaining ventilation This is especially true in wedge or segmental resection where there may be a large area of raw bubbling lung surface at the end of surgery despite maximum care in suturing The use of intermittent positive pressure breathing at a pressure of 10 cm of water may be sufficient for therapy without increasing the air leak

Physiological Therapy in Inoperable Neoplasms—There is a general

therapeutic nihilism in patients when it has been decided that surgery is not possible In many centers it is true that chemotherapy and radiation therapy are used The care of the patient appears to devolve upon the specialist in such therapy rather than upon the physician trained in physiological management As a result such therapy is often used terminally rather than in alleviating pulmonary dysfunction early in its evolution A tumor obstructing a major portion of a lung may be causing the patient considerable dyspnea The treatment of such a tumor with subsequent partial reopening of a bronchus offers the patient at least *a period of comfort It is important to consider the use of these techniques* wherever physiological dysfunction is found of sufficient degree to cause the patient symptoms The tendency to await signs should be *resisted Moreover the effects of therapy can be ascertained in most* cases by using simple pulmonary function tests Thus the physiologist in addition to regarding radiation therapy and chemotherapy as aimed at the neoplastic cells themselves looks on them as aid to pulmonary function

The harmful effects of radiation upon the lung are considerable chemotherapy has not this disadvantage Radiation fibrosis may alter pulmonary function and produce an increased pulmonary disability The

perfused and hence useful to the economy the total gain from radiation may be such as to offset any loss Where obstruction is developing because of extrinsic lesions the need becomes even greater *It must be* remembered that dyspnea may far precede the presence of clinical stridor

Physiological therapy in relation to residual function must be considered *Many patients with inoperable neoplasms* have been made considerably more comfortable by the use of a regimen of bronchodilators with intermittent positive pressure breathing in full knowledge that the treatments are purely palliative It is essential to treat the symptoms of such patients and often this therapy has a markedly beneficial effect When mucus is a problem corticoids and antibacterial agents used together may be immensely valuable and may prolong comfortable life The patient s well being must be considered *not only* as it is affected by the tumor but also from the point of view of improving the pulmonary function

SUMMARY

Tumors of the lung affect pulmonary function to a great degree according to their position extent and structure The majority of such tumors occur in patients of the age group where degenerative pulmonary disease is common Simple methods of evaluation of pulmonary function give therapeutic guidance in the majority of these cases

Surgery for tumors may be made safer by physiological evaluation *and the patients disability may be lessened by physiological therapy* Moreover, indications for palliative therapy may frequently result from physiological study

Consideration of tumors must include the effects on cardiorespiratory function as well as the natural history of the particular tumor

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Chapter 11

Surgical Treatment

THOMAS H. BURFORD, M.D., and THOMAS B. FERGUSON, M.D.

HISTORICAL

ON April 5, 1933, Evarts Graham did the first successful one-stage radical pneumonectomy for bronchiogenic carcinoma. This event marked the beginning of an era giving hope to the hitherto hopeless list of victims of this disease and at the same stroke giving enormous impetus to the development of the entire specialty of thoracic surgery. This patient is alive and well 25 years later—strong testimony that our surgical treatment for lung cancer is sound and that the present low curability rate is related not to the form of treatment but to delay in diagnosis. Prior to 1933 attempts to treat lung cancer consisted of piecemeal removal of the tumor, or drainage of an abscess distal to an obstructing endobronchial mass. After 1933 technical advances came more rapidly. Graham showed that abrupt ligation of the pulmonary artery is not followed by the fatal consequences that are seen with massive pulmonary embolism, a point of considerable concern at that time. Rienhoff was the first to stress the importance of individual ligation of blood vessels and bronchus rather than mass ligation of the hilum. He also pointed out that total removal of the lung need not be followed by a thoracoplasty to obliterate the empty space since compensatory bodily adjustments, including mediastinal shift, elevation of the diaphragm, and contraction of the chest wall, take care of the space problem. Today thoracoplasty following pneumonectomy for cancer is rarely indicated. To find the proper way of managing the bronchial stump following resection was most important, since operative morbidity and frequently mortality are directly related to the incidence of bronchopleural fistula. It took the combined experience of many thoracic surgeons to demonstrate that successful bronchial closures require careful mucosa to mucosa approximation with dependable sutures while avoiding the use of crushing clamps and excessive disturbance to the bronchial blood supply. Churchill showed that the incidence of fistulas is less when the accurately sutured stump is covered with a flap of viable pleura. Other knowledge that has contributed greatly to the continuing decline in mortality include advances in thoracic anesthesia, blood replacement techniques, cardiac

and pulmonary physiology and antibiotics Today the surgery for lung cancer is universally performed at a mortality risk below 10 per cent This is a remarkable achievement to have eventuated in less than a quarter of a century

SURGICAL ASSESSMENT OF THE PATIENT

Once the diagnosis of cancer is established it is the co responsibility of the internist and the thoracic surgeon to evaluate the patient carefully and decide whether surgical exploration is indicated In some cases this decision is easy to make in others it is very difficult There are two main aspects to be considered Thoracotomy may be contraindicated in a resectable lesion by a coexisting medical disorder or may be contra indicated because of the presence of certain extrathoracic or intrathoracic metastases from the primary tumor These criteria of inoperability as they are sometimes called are discussed as medical criteria and meta static criteria

Medical Criteria —Because lung cancer is primarily a disease of older individuals there are a number of derangements of other organ systems which can complicate the operation and the postoperative period but actually are very few which contraindicate operation The aid of the internist is invaluable in bringing the difficult case into optimum condition for surgery Disease of the cardiovascular system are frequently present but only two should delay a needed thoracotomy These are coronary *occlusion with infarction occurring within the previous two months* and overt heart failure Almost all older patients who come to surgery have electrocardiographic changes suggestive of coronary artery disease and many of them have a clinical history of infarction in the past However if they are stable at the time of surgery and are managed carefully after wards the majority will have no trouble Patients with heart failure that do not respond to vigorous treatment such as occurs with advanced rheumatic valvular lesions are not surgical candidates Patients who have failure on the basis of arteriosclerosis can usually be compensated with a good cardiac regimen and then operation carried out safely Hypertension does not preclude operation unless it is in the malignant phase

The evaluation of concomitant disease of the respiratory system notably emphysema can be most difficult Emphysema in the older patient is either of the diffuse cystic type or the localized bullous type while emphysema in the younger individual usually accompanies asthma There have been numerous tests devised in an attempt to quantitate respiratory disability These include vital capacity maximum breathing capacity functional residual capacity bronchospirometry and pulmo nary artery catheterization Unfortunately no test or group of tests is

reliable enough to predict accurately whether any given patient will tolerate resection without difficulty or will be left a respiratory cripple, so the final evaluation and decision must be made on clinical grounds The degree of overdistension of the lung can be fairly reliably estimated by looking for cystic change on the films noting the antero posterior chest diameter, and checking the position and excursion of the



Fig 136—Cancer at the hilus of the right lung in a patient with severe bullous emphysema

diaphragm by fluoroscopy (Fig 136) The amount of dyspnea may be out of proportion to the functioning lung tissue because of chest wall pain, pleurisy, or wheezing caused by a strategically located tumor The estimate of post resection disability must be carefully related to the preoperative situation A patient with a small nonobstructing tumor may be more uncomfortable after pneumonectomy than the individual who is quite dyspneic preoperatively because the tumor has made an entire lung atelectatic In fact, the latter patient is quite likely to be improved

by removing the functionless lung A useful clinical test is to have the prospective operative candidate perform an exercise such as walking rapidly along a corridor or up a flight of stairs and then check the pulse and respiratory rate and compare his response to a normal individual's response to the same exercise Taking all these factors into consideration deciding whether or not operation should be done at times requires the best in clinical judgment Even so occasional unfortunate individuals will be left respiratory cripples by surgery

Other general factors such as age and nutritional status are by themselves not contraindications but the final evaluation must be a total assessment of the patient An elderly man with emphysema and heart trouble might be too great an operative risk whereas if these factors were to occur singly operation might be safe

Metastatic Criteria —*Extrathoracic* —A careful search for distant metastatic lesions is always necessary Predominant sites of metastases are the supraclavicular lymph nodes the brain the adrenal glands and bone

If palpable nodes or scalene fat pad nodes in the neck are found to be positive on biopsy it is generally agreed that cure is not possible However in this situation palliative resection is frequently done if the patient is young or if the primary tumor is serving as a septic focus

Symptoms referable to the central nervous system such as blurring of vision headache nausea or vertigo should be carefully evaluated by a consulting neurosurgeon Electroencephalograms and cerebral air studies will in many instances reveal evidence of multiple cerebral metastases making surgical treatment of the chest lesion unwise If a solitary cerebral metastatic lesion is found and there is no evidence of other intrathoracic or extrathoracic spread of tumor the patient then deserves craniotomy for removal of the solitary metastasis and later a thoracotomy for control of the primary lesion Of course the number of cases that can be salvaged in this manner will be small However one of us (T H B) has 1 case that is well and free of disease 8 years after this combined management

Metastases to the adrenal glands are difficult to prove but may be suspected if the patient has persistent weakness and hypotension At times the patient may present the typical picture of Addison's disease As a general rule patients with adrenal metastases have other metastatic lesions which help to rule out operation

Metastases to bone generally are heralded by the appearance of bone pain a deep unrelenting "bursting" type of pain *Favorite sites are the* spine and pelvis Careful x ray surveys are indicated in any lung cancer patient who has persistent bone pain The differentiation from arthritis sometimes is difficult The alkaline phosphatase is of little value Many times the films of the area will be negative if the metastatic lesions are early in which case small doses of x ray therapy may help with the

by inflammatory nodes while aortic aneurysm, elevation of the left main stem bronchus, and left atrial enlargement are other conditions which may cause recurrent nerve paralysis If either nerve is involved separately by a known tumor, exploration is still indicated A portion of the phrenic nerve can be resected along with a rectangular piece of pericardium to give a clean dissection When the recurrent nerve is involved the tumor extension usually makes complete resection impossible, but a few long term survivals have been reported When both nerves are paralyzed in the same patient, operation is not indicated because there are no reported cases of long term survival in such individuals

The pulmonary vessels are the most frequently involved mediastinal structures The overwhelming majority of nonresectable cases are inoperable because of involvement of the pulmonary artery or veins too near their origin There is no reliable method of ascertaining this except through thoracotomy. Vessel involvement may be suggested by the presence of enlarged hilar nodes on x ray (Fig 137), or angiocardiography may show vessel involvement, but neither of these is sufficient evidence to withhold thoracotomy and risk missing a resectable lesion

If the tumor extends outwardly, the pleura and chest wall will become involved Pleural seeding causes an outpouring of blood tinged fluid from which tumor cells can easily be recovered, and their presence is a contraindication to surgical resection Direct extensions through the pleura into the chest wall proper are harder to detect If the patient complains of pain in the chest on the side of the lesion, particularly if there is anterior radiation, involvement of the intercostal nerve should be suspected Relief with an intercostal nerve block will confirm the diagnosis Detail films of the ribs adjacent to a peripheral tumor should be examined for rib erosion (Fig 138) If a chest wall mass can be felt, a tissue diagnosis can later be obtained by needle or incisional biopsy This should only be done if the patient is otherwise inoperable Opinions differ as to how large an area of chest wall can be removed *en bloc* with the lung, but most surgeons feel that removal of adjacent portions of involved ribs and intercostal bundles is justified if the patient is in good condition, and the area of involvement is not so large that resection leaves an unmanageable defect Stabilization with stainless steel screen or tantalum mesh has been described, but for the most part survival in such patients is very limited because of the extensiveness of the tumor The direct extension of a peripheral upper lobe cancer into the apex of the thorax to involve the first rib, the brachial plexus, and the sympathetic nerve chain causes the symptom complex of the Pancoast syndrome, consisting of radiating pain in the arm and shoulder and a Horner s syndrome on the involved side These cases, if proved to be caused by cancer, are inoperable Palliation with x-ray therapy is generally very good Exploratory thoracotomy may be necessary for

diagnosis because the same picture on rare occasions can be caused by apical tuberculosis

Involvement of the diaphragm by tumor may cause recurrent or intractable hiccoughs This is not a sign of inoperability because a large segment of the diaphragm can be removed with the lung if necessary In most instances the resulting defect can be closed primarily but if not may be bridged with a dermal graft polyvinyl sponge or other prosthetic material

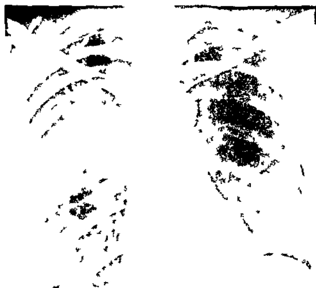


Fig 138—Peripheral carcinoma on the right with involvement of the chest wall and osteolytic destruction of several ribs

Interpretation of suspicious areas in the contralateral lung must be done with great care Spread of tumor to the opposite lung takes place either in the form of lymphangitic permeation or discrete nodulation Lymphangitic spread is easy to recognize as is nodulation when the nodules have reached large size (Fig 139) An otherwise operable patient should not be refused thoracotomy on the basis of one or two small rounded shadows in the good lung unless recent origin or rapid growth can definitely be demonstrated for these shadows may be benign lesions or vascular configurations

In summary the decision regarding surgery in a given patient with proved intrathoracic or extrathoracic metastases is based on our total

surgical experience to date with each type of malignant extension not only in terms of numbers of long term survivals but also in terms of whether the required operation leaves the patient in a worse state than he would have been without surgery If careful due consideration is given to the details of each case this decision can be made fairly in the vast majority of patients *We feel that if a patient is borderline in some respect* or the evidence for metastases is not conclusive this patient deserves to have a thoracotomy and a chance for cure rather than being designated as a hopeless case without absolute justification



Fig 139—Cancer of the right lung with lymphangitic and nodular bilateral metastases

PREOPERATIVE PREPARATION

Once the decision to operate has been made and a general medical evaluation has been done there is little that is necessary in the way of preparation for surgery If sepsis with fever has been part of the picture *a preliminary course of antibiotics should be given* If sputum production is large it should be reduced by postural drainage and the administration of nebulized mixtures of antibiotics and bronchodilators We are

of the opinion that all older patients with evidence of diffuse nonspecific myocardial disease should be digitalized preoperatively This is especially true if total pneumonectomy is a likely possibility The abrupt reduction in oxygenating surface plus retained secretions in the early postoperative period often lead to myocardial hypoxia which becomes clinically manifest in rapid auricular fibrillation Preoperative digitalization does nothing to prevent the onset of fibrillation but the digitalized patient will fibrillate at a slower rate where blood pressure and circulatory integrity will be maintained whereas the undigitalized patient with rapid fibrillation will often go into cardiovascular collapse and pulmonary edema

The importance of proper anesthesia given by a competent anesthesiologist cannot be overemphasized The increased safety of thoracotomy is in large measure due to our increased knowledge of respiratory physiology and anesthesia The anesthesiologist has many things to watch for and to do The level of anesthesia must not abolish the cough reflex and yet must be deep enough to allow manual control of respiration at all times Removal of secretions by suction as they accumulate is vitally important and the patient who is "wet" throughout operation should be bronchoscoped at the end of the procedure Adequate manual ventilation of the lung is necessary to prevent the development of respiratory acidosis which is difficult to detect when the patient is getting high oxygen mixtures and carbon dioxide accumulation is not accompanied by hypoxia and cyanosis A discussion of the various anesthetic agents being used to achieve these results and carry the patient safely through operation is not within the scope of this chapter but the necessity of having proper anesthesia will be echoed by every thoracic surgeon

SURGICAL TECHNIQUES

It is not our intention to discuss specific technical details of removing a lobe or a lung These are well described in many papers and books on the subject

Only in very few cases of lung cancer does the surgeon know preoperatively what procedure will be required An adequate surgical procedure is one that removes the tumor and as much of the lymph drainage pathways as surgically feasible Many cases are of an explora tor- ent For this reason by far the erolateral thoracotomy with res The incision curves around the scapular angle and extends anteriorly along the course of the rib and the pleural cavity is entered through the rib bed This approach gives safe adequate exposure for any procedure that might have to be done The use of intercostal incisions is discouraged because of the

limitation of exposure Two other principal approaches to the lung have been described, and each has its proponents These are the anterior thoracotomy and the prone thoracotomy Anterior thoracotomy has been advocated for poor risk cases because there is less circulatory and respiratory compromise in this position An adequate resection can be done with this exposure, but it is less safe because emergency control of hilar structures is more difficult In the prone thoracotomy the operated side is dependent It was introduced primarily for use in cases of bronchiectasis, where the secretions are copious In cancer this is rarely the case In the prone position there is less chance of flooding the uninvolved lung with secretions from the operative side, and respiratory acidosis is said to be easier to control The disadvantage is again lack of adequate exposure for every situation

When the chest is open the situation is appraised and a decision made as to what can be done Most of the cases that are nonresectable will have tumor invading the pulmonary vessels at the hilum If the situation appears hopeless, the pericardium should be opened, for occasionally enough vessel length will be present intrapericardially for safe ligation If the phrenic nerve is involved, a segment of pericardium can be removed with the tumor The presence of nodes in the subcarinal region or along the trachea should not deter resection, for these node-bearing areas can be removed, in some cases relatively cleanly In peripheral tumors which involve the chest wall or diaphragm the lung should not be peeled away from the adherent area, but if the decision is to resect, the hilar structures should be divided and the lung or diaphragm dissected *en bloc* A generous margin of normal tissue away from the area of invasion must be removed In the chest wall this amounts to a rib and intercostal space above and below the growth

The problem of obtaining tissue at exploratory thoracotomy for frozen-section diagnosis frequently arises It is preferable that biopsy be obtained without cutting into the tumor to minimize the chance of dissemination of malignant cells In many instances, however, this is not possible, and frequently the only way to differentiate between cancer and organizing pneumonia is to excise a wedge of tissue and close the defect with sutures, taking care to drape off the biopsy area and discard
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looped with ligatures and the main stem bronchus cleared of tissue at the contemplated line of resection before any vessels are tied This will establish beyond doubt that the lesion is resectable The vessels are tied right at the pericardium usually the artery first The level of bronchial resection should always be at the tracheal bifurcation so that no blind pocket remains The proximal bronchus should not be handled or clamped in any way It is closed with fine interrupted silk sutures which draw forward and approximate the posterior membranous bronchus and the anterior cartilaginous portion The closed bronchus is tested for leaks with saline and then covered with a rectangular flap of pleura which *remains intact along one margin to assure viability This* technique removes all the lymph nodes at the hilar level Subcarinal and paratracheal nodes must be removed separately After pneumonectomy has been completed the cavity is rinsed out with saline particularly if the tumor has been exposed in taking a biopsy The chest is then closed without drainage and after the patient has been returned to the supine position the pressure in the pleural space is adjusted slightly to the negative side

Variations or extensions of the standard pneumonectomy have not altered cure rates significantly Kirklin has described the routine use of intrapericardial ligation of the pulmonary vessels Watson has outlined the technique of a so called radical pneumonectomy in which the subcarinal and paratracheal tissues are removed *en bloc* with the lung In practice this is difficult to accomplish for frequently there is not enough tissue around these nodes to effect a true block removal Also the incidence of bronchopleural fistula is increased because of the extensive stripping of the bronchial blood supply the procedure entails Gronqvist in a study of 16 cases of combined lung and chest wall resections found that the only long term survivors were those in whom the chest wall extension was still limited to involvement of the parietal pleura This would indicate that extensive chest wall removal is unjustified There have been sporadic reports of extended survival in cases usually classed as inoperable by the accepted criteria Chardack reports a 5 year survival after radical resection and x ray treatment for a superior sulcus carcinoma These unusual cases do not indicate that these lesions necessarily should be treated surgically however for the growth pattern of tumors is too unpredictable Every large thoracic surgical service has on file 1 or 2 cases of proved cancer that survived 5 years even though no treatment *was given and Blades and McCorkle have reported* the spontaneous regression of a bronchiogenic carcinoma

The question of doing lobectomy rather than a pneumonectomy for small peripheral carcinomas has been debated for a long time Most surgeons are of the opinion that the best opportunity for curing cancer is to do a large operation for a small tumor These surgeons do lobec-

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to proximal stump will at times enable the surgeon to save a lobe Bronchial adenoma is a malignant tumor however and must be totally extirpated With epidermoid carcinomas adenocarcinomas and undifferentiated tumors the standard wide resection should be done

In the earlier days pneumonectomy was accompanied by concomitant or delayed thoracoplasty as a routine It was later shown that nature would take care of the space problem but at the expense of causing some degree of overdistension of the remaining lung In the patient with a low respiratory reserve a thoracoplasty done about 10 days after resection may prevent the later changes of overdistension and cor pulmonale It is not recommended for all cancer cases however because the low percentage of long term survivals does not justify its routine application

SURGICAL PALLIATION

There are a number of ways in which the patient with incurable lung cancer can be helped surgically Resection can be done leaving some areas of unresectable tumor This type of surgery is certainly justified if there is reasonable assurance that bronchopleural fistula or infection will not occur that is if the level of resection is a relatively "clean" one Removal of tumor at all costs or resection of large portions of the tracheal wall or auricular wall is not good palliative technique If it is found that the patient cannot be cured lobectomy rather than pneumonectomy should be done if possible Lobectomy in peripheral cavitary tumors will give marked relief by eliminating the fever and foul sputum Pleural metastases with effusion cause dyspnea and drain the body protein stores and should be treated with intrapleural injections of nitrogen mustard or radioactive gold If this method fails thoracotomy with removal of the parietal pleura is a highly successful way to control fluid formation Chest wall pain from tumor invasion can be relieved by intercostal nerve neurectomy Intractable singultus from diaphragm or phrenic nerve irritation can be eliminated by cervical phrenicectomy Surgical palliation for the superior vena caval syndrome bypassing the area of block with an arterial heterograft has been described by Ashburn

POSTOPERATIVE CARE

Postoperative care after pulmonary resection for cancer is no different than after resection for benign disease except that more close supervision is required since a majority of the patients are in the older age group Removal of secretions is vitally important either by cough or by periodic endotracheal catheter suction (Fig 141) Patients with borderline respiratory function should have a tracheotomy done Bronchodilators and mucolytic agents in nebulizer form will aid in raising secretions If

excessive chest wall pain prevents effective cough, intercostal nerve blocks should be done rather than depress an elderly patient with excessive narcotics After pneumonectomy position of the trachea is important, and any significant shift detected clinically or by x ray examination must be corrected by removal of fluid or air Oxygen should be given during the early postoperative period to assure optimum oxygenation of the myocardium If cardiac arrhythmias do occur, the patient should be rapidly digitalized if this was not done preoperatively Frequently, as the oxygenation is improved, the rhythm will spontaneously



FIG 141 —Method of catheter aspiration of the trachea

revert to normal If it does not within a few days quinidine should be used High fever can be controlled primarily by vigorous measures to keep the lungs clear of secretions Elderly patients tolerate excessive elevations of temperature poorly, and at times it is necessary to bring the temperature down rapidly by the use of aspirin or alcohol spongings When surgery is performed in the summer the use of a cooled oxygen tent is of great help in preventing hyperthermia

Gastrointestinal and fluid balance problems are usually not seen after pulmonary surgery Acute gastric dilation occasionally occurs which is manifested by progressive shortness of breath and tachycardia, and there even may be cyanosis and lowered blood pressure With gastric suction the patient will very quickly recover Care should be taken

not to give too much blood and intravenous fluid in the early postoperative period because of the possibility of inciting pulmonary edema. As a general rule all patients who have pulmonary resection do better and have fewer secretions if they are kept a bit on the "dry" side.

There is no question that the incidence of pulmonary complications after lung surgery has been lessened by the routine use of antibiotics. We feel that the combination of penicillin and streptomycin for 5 to 7 days after surgery is good prophylaxis.

RESULTS OF SURGICAL THERAPY

The technical advances that have been made in pulmonary surgery during the past 25 years are mirrored in the diminishing operative mortality rates. During the period 1933 to 1940 the mortality from pneumonectomy hovered around 50 per cent. From 1940 to 1950 Rienhoff reported a mortality rate of 24 per cent. Since 1950 it has continued to decline. Kirklin and Clagett report 6.9 per cent operative deaths in a group of 233 cases done during 1951, 1952, and 1953. The rate at the Barnes Hospital, St. Louis, Missouri, for the same three-year period was 8 per cent.

The figures for overall cure rate of lung cancer, on the other hand, have shown a discouraging lack of improvement. Table 17 points out

Table 17

Source	*Tulane*	*Jefferson*	*Mayo*	*Overholt*	*Barnes*	*Total*
Period	1937–53	1946–53	1943–49	1932–51	1948–55	
No. Cases	1170	532	767	733	1008	4210
Per Cent Explored	52	71	48	62	60	59
Per Cent Resected	33	39	24	37	35	34
5-yr. Survival						
% of all Resections	14	22	—	21	21	19
% Resected for Cure	31	42	37	34	39	37
% of Total Cases	8	9	6	8	9	8

several reasons. Out of a total of 4,210 cases collected from 5 large clinics only 59 per cent were explorable. This means that 41 per cent of the patients already had some criteria of inoperability when first seen by the surgeon. *A further 25 per cent were non-resectable at the time* of exploration, so that ultimately only 1 patient out of 3 (34 per cent) had a lesion which was resectable. A breakdown of these percentages in recent years does not indicate that the size of this inoperable group is diminishing. In Overholt's series the average time lag from the initial manifestation of the tumor, either symptom or x-ray shadow, to thorac-

otomy varied from 6 7 months to 11 5 months During the last 10 years this delay period has not shortened as one would have a right to expect with the increasing use of x-ray, cancer education, and other factors, but has actually lengthened somewhat because of the confusing symptomatic improvement frequently seen with antibiotic therapy Five-year survival figures throughout the country are about the same Of the contracted group of patients who are explorable and resectable for cure, about a third can be expected to be alive at the end of 5 years When resection for cure and for palliation are grouped together about one fifth of the patients will survive 5 years This number of survivors represents only 8 per cent of the total cases seen at the outset The widespread use of chest films, a high index of suspicion and early thoracotomy will serve to give more of these unfortunate individuals a chance for surgical care

Studies relating the histological cell type to survival show that epidermoid carcinoma had the best prognosis of all excluding bronchial adenoma Kirklin *et al* found that 12 per cent and 11 per cent of epidermoid and adenocarcinomas, respectively, survived 5 years, whereas only 0 8 per cent (1 patient out of 121) of the small cell cancers lived this length of time Overholt reviewed 51 patients that survived 5 years after surgery and found the same favorable trend with squamous cancer, but also noted that in 9 of the 51 patients, or 18 per cent, the tumor was undifferentiated, indicating that even this histologic type of tumor is surgically controllable

One phase of treatment which has not been fully explored is whether combinations of therapy, *i e*, surgery and high voltage roentgen therapy, or surgery and intravenous nitrogen mustard therapy will improve the survival rate over that for surgery alone

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Chapter 12

Radiotherapy

HAROLD W JACOX, M D

RADICAL surgery, whether by lobectomy or total pneumonectomy, is generally accepted as the most hopeful means of a permanent cure for bronchiogenic carcinoma But surgery is applicable only to a small proportion (of the apparently increasing number) of patients with this disease Moore reviewed 370 case records from the Columbia Presbyterian Medical Center, in New York City for the 10 year period from 1940 through 1949 Eighty-seven (or 23 5 per cent) underwent resection Of the 31 patients resected prior to 1946, 4 were alive in 1950—a 13 per cent 5 year survival rate Of those patients who undergo resection, a sizable number will later have local recurrence or distant metastases and will be candidates for radiotherapy Other writers have reported similar experiences

Radiotherapy is bound to play a secondary role in the management of this disease since the usual treatment is complete surgical removal based on early diagnosis Radiotherapy is important, however, as an attempted curative measure for those whose medical condition will not permit surgery, and as a palliative measure in the other instances For example, records of 33 patients who, although selected on criteria for operability, received radical radiotherapy only, showed a survival rate comparable to surgically treated cases (Smart and Hilton). In another instance involving 66 patients with carcinoma of the bronchus, a clinical experimental attempt to combine radiotherapy with later resection resulted in the tumor being eradicated from the chest in nearly half the cases, although there was a high incidence of empyema and bronchopulmonary fistula (Bromley and Szur) Such evidence shows that irradiation can locally "sterilize" a significant proportion of operable lung cancers, but when distant metastases are considered, the total results indicate no improvement This conclusion has also been reached by others In a "control" group of 125 patients from the Mayo Clinic (Leddy *et al*) who were treated with neither roentgen therapy nor resection, none lived longer than 1 year after the diagnosis was made In another group of 125 inoperable patients treated with *x*-rays, 25 lived 1 to 12 years after the diagnosis The value of radiotherapy as a palliative measure in this group of 250 patients with proved primary bronchiogenic carcinoma is self-evident

PALLIATIVE THERAPY

Although it begins dealing with the disease in an advanced and unfavorable state, radiotherapy is a valuable palliative measure, the most effective of all for symptomatic relief. Cough, expectoration, hemoptysis, pain and dyspnea may all be relieved in varying degrees by radiation. Relief of hemoptysis *is frequently obtained*, although it occasionally returns. Cough is nearly always lessened and sometimes relieved. Relief of dyspnea is *more variable*. Also hilar, mediastinal and peripheral lymph nodes may be reduced in size; a superior vena caval compression syndrome may be relieved; obstructive pneumonitis may be resolved; parenchymal infiltration may be diminished; pathological neoplastic fractures may be healed; and a feeling of well being may be restored. This is similar to what happens in many other conditions—such as cardiovascular, renal and neuropsychiatric disorders—for which only palliation can be expected.

METASTATIC LESIONS

The pain of osseous metastases is usually relieved by a short intensive course of daily roentgen therapy requiring about 2 weeks, and in some instances recalcification of bone destruction occurs. Pain due to direct osseous extension of the neoplasm is less constantly helped. Patients with pleural effusion are improved only occasionally. *Response to* intrapleural introduction of radioactive colloidal gold or nitrogen mustard to help retard the re-accumulation of fluid is variable. If the initial general condition of the patient is poor, there is little likelihood of much palliation from any form of radiation. Also it is usually impossible beforehand to tell which patients are likely to have good symptomatic response or long survival. Intracranial metastases, quite frequent in this disease, are often dramatically reduced to an asymptomatic status.

Some radiotherapists believe that—within tissue tolerance limitations—the larger the dose, the longer the survival, but this is difficult to prove. Craver analyzed results obtained in treating 142 patients with roentgen rays and 14 with radon or radium element pack and found the roentgen radiation more effective than radium. He noted that, as the tumor dose

Five years survival occurred in 8.3 per cent; 1 survived 12½ years; 2, 4½ years; 1, 3 years; 1, 2 years; 1, 18 months; 5, 6 months; and 8 less than 6 months. It is generally believed that the higher the tumor dosage, the greater the palliative effect. Good palliation is seldom achieved unless the dosage is at least 2,000 r and is uncommon with doses of less

and skin reactions are no longer a problem For localized squamous cell carcinoma an attempt is made to deliver a tumor dose of 5,000 to 5 500 r usually within 7 to 8 weeks through multiple portals For anaplastic carcinomas a 4,000- to 4,500 r tumor dose covering the entire mediastinum is given in the same or slightly less time Although the palliation may be greater, the biological effects and the number of survivals are about the same as with conventional voltage range and methods This means that patients can be treated about as well in community hospitals lacking supervoltage therapy as they can in larger medical centers Nothing can be gained by supervoltage therapy that cannot be obtained by careful planning and treatment application at deep therapy voltages In radical treatment a circumscribed growth is exposed to localized high dosage in the double hope that the growth may be destroyed and that no metastases exist Radical irradiation usually means an intensive daily course of treatment to a tumor dose of 5,000 to 6,000 r over a period of from 4 to 6 weeks This may result in less constitutional reaction, and the risk of damage to neighboring structures such as the heart and esophagus may be greater When the treatment fails to control the disease, life may be shortened because of the severe damage to the tumor bed and the loss of resistance to the growth However, in those patients who develop pulmonary radiation reactions, symptomatology usually can be controlled by cortisone or Meticorten in proper dosage Where the indication is for wide coverage of primary tumor and regional metastases, the local dosage must be lower and the technique less exacting, so that there is no advantage gained from megavoltage therapy Palliative treatment may be indicated even in the presence of generalized metastases where local masses are causing pressure effects and some growth restraint can be expected Even with the most careful handling some constitutional effect of treatment is inevitable, and the change and degree of benefit must be carefully weighed when deciding whether to treat at all in advanced cases The discomfort and time required for treatment must be balanced against the expected duration of life and the degree of likely benefit Unfortunately, supervoltage radiation offers nothing curative in lung cancer, although there is evidence of significant palliation Traces of primary tumor were found at autopsy in each of a small series of patients who received tumor doses of from 3,500 r to 7,500 r in 18 to 35 days (Watson) There is no difference in the cancerocidal effects of 2,000 Kv, radium, cobalt^{60}, or 250 Kv radiation From the standpoint of response to radiation, cancer of the lung is really several diseases rather than a single disease The squamous-cell type of cancer of the lung is presumed to be as sensitive as squamous-cell cancers in other parts of the body, but because of the nature of the lung tissue, *i e*, the tumor bed will not tolerate an intense radiation effect

LIMITING FACTORS

The danger of pulmonary fibrosis has always been the limiting factor in prescribing radiotherapy much larger doses can be sustained by other tissues. An exception to this rule has recently been demonstrated, when damage to the muscular coats of the esophagus was found following reasonable dosage by the betatron to an adjacent lung lesion (Seaman and Ackerman).

CHEMOTHERAPY

Although nitrogen mustard (HN) does have some retarding effect on poorly differentiated or oat cell types of lung cancer this effect is not curative and is usually short lived over a period of 1 or 2 months. Biologically and histologically the effects of nitrogen mustard are cytotoxic and similar to those produced by radiation and sometimes both treatments have been used together. The survival of patients treated with roentgen rays *and* nitrogen mustard has been found to be slightly longer than those treated with either one alone. However this combination is not curative either and may seriously depress the bone marrow. In case of acute severe compression of the superior vena cava nitrogen mustard advantageously may be given initially to get prompt regression of swelling it is then followed by a complete course of irradiation.

Many possible radiation sensitizers have been tried recently in an effort to increase the efficiency of radiation therapy of lung tumors but so far this work has not had any spectacular success in human cancers.

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Chapter 13

Adenoma and Cylindroma

WHILE the cause for the sudden appearance and high incidence of *cancer* of the lung is debatable the reason for the abrupt emergence and growing incidence of *adenoma* of the lung has as yet evoked no argumentation It is universally admitted that this "new" disease owes its "discovery" to the new diagnostic method bronchoscopy However the reason for the failure in the past on the part of pathologists to recognize at postmortem examination this presumably "eye catching" tumor has never been explained It can be conjectured that because of a lack of knowledge on the part of the clinician the pathologist was not afforded the opportunity of observing cases after death Another possibility is that the severe lesion of the lung to which patients with adenoma of the bronchus usually succumbed absorbed pathologists to such an extent as to divert their attention from the bronchial polyp" The dictum attributed to Goethe that we see only what we know may be aptly applied in this case As a matter of fact tuberculosis of the larger bronchi which occurs in tuberculosis of the lungs with considerable frequency was identified first by clinicians and bronchoscopists and only much later by pathologists

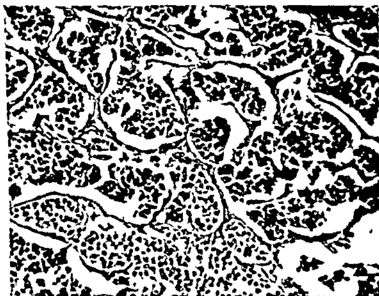
Although bronchial "excrescences" of a polypoid nature were mentioned by Laennec in his treatise on auscultation credit for the first description of adenoma of the bronchus belongs to Mueller In 1882 he discovered the tumor during an autopsy on an individual who had died of an extensive unilateral bronchiectasis accompanied by a putrid infection of the lung Mueller pointed out that the disease of the lung had resulted from the obstruction of the bronchus by the polypoid new growth

Yankauer described 2 cases treated by him one in 1922 and another in 1929 The latter case concerned a man 30 years of age who had developed a stubborn pain in the right side of his chest The patient was subjected to phrenicectomy with some relief from the pain but not from the cough Bronchoscopy revealed a grayish pedunculated neoplasm occluding the bronchus of the right middle lobe The tumor was removed bronchoscopically resulting in cure

Patterson found that 26 cases of this type had been reported up to 1930 16 of which had been diagnosed during life and 10 at autopsy Kramer and Som found that bronchial adenoma occurred in 6 per cent

PLATE I





BRONCHIAL ADENOMA

A. [illegible] pedunculated [illegible] projecting upward toward the trachea.
B. [illegible] structure of the adenoma.

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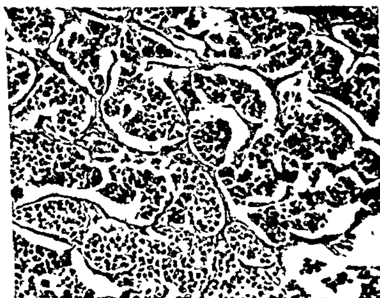
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PLATE I





BRONCHIAL ADENOMA

A Cut surface of the lung [illegible] showing [illegible] (carcinoid type) projecting upward toward the trachea

B Histological structure of the adenoma

of all bronchial tumors and Clerf and Bucher observed adenomas in 12 per cent of their cases. Churchill stated that the ratio of bronchial adenomas to bronchial carcinomas unproven microscopically is 1 to 20 and the ratio to bronchial carcinomas proven microscopically is 1 to 10.

Of all the benign bronchial neoplasms adenoma is probably the most common.

HISTOGENESIS

It is universally accepted that adenoma is a neoplasm of bronchial origin but the particular cell from which it starts remains a matter for speculation. Some observers have traced the origin to the cells of the bronchial mucous glands, others to the cells lining the excretory ducts of the glands, and still others to the basal cells of the bronchial mucosa. Womack and Graham have stated that bronchial adenoma originates in *anlages* that have failed to develop normally. In their opinion there exists a similarity of behavior and in some respects of origin of bronchial adenoma to the mixed tumors of the parotid gland. Accordingly the adenomas were designated by them as mixed tumors of the lungs.

TYPES

There are many varieties of bronchial adenomas but the following two are of particular clinical interest because they are most frequently encountered. They are:

1. The carcinoid type
2. The cylindroid type

Carcinoid Type—Histological Structure.—The tumor is defined as carcinoid because of its histological resemblance to carcinoid tumors of the small bowel. An adenoma of this type is composed of somewhat oval or oat shaped cells which resemble the oat cells in bronchiogenic cancer. The nucleus almost entirely fills the body of the cell. The cells are arranged in a quasi acinar fashion piled up in several layers with barely perceptible lumina. The structure of the stroma depends upon the age of the tumor. In younger tumors it is made up of fine fibers running between the clusters of cells; in older adenomas there occur wider areas of fibrosis scattered throughout the tumorous section. Still older adenomas show areas of necrosis, ossification and hyalinization. The growth is richly vascularized.

Adenomas of the carcinoid type are surrounded by a thin fibrous capsule which is covered by a metaplastic epithelium of the bronchial mucosa in the intrabronchial component. The neoplastic cells have not been observed in mitosis nor have they been known to invade the capsule (Figs. 142 and 143).

Cylindroma Type.—Microscopically, the tumor imitates the *histological* pattern of a colloid goiter. It is made up of cuboidal or flattened epithelial cells which are arranged in two layers and form interwoven coil like structures of cylinders (hence the term "cylindroma") that contain a homogeneous hyalin and mucoid matter. Cells in mitosis are occasionally found



Fig. 142.—*A* endobronchial adenoma (arrow), *B* a cross section of entire tumor walled off by the cartilageous ring at the base

Macroscopically, the cut surface of the neoplasm has been likened to the pattern displayed by the cut surface of Swiss cheese *Like the carcinoid type, the cylindroid type is surrounded by* a fibrous capsule Cylindromas *resemble some types* of mixed tumors of the parotid gland (Fig 144)

Macroscopic appearance—The gross appearance of carcinoid and cylindroid tumors is almost alike (Fig 150) A cardinal feature of the carcinoid type lies in the tendency of a great majority *of these* tumors to advance in two directions (1) *toward the lumen of* the *bronchus (intraluminal) and* (2) *toward* the parenchyma of the lung (intrapulmonary) Thus, an hourglass or dumbbell like growth is

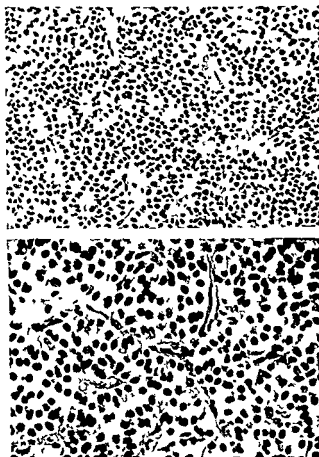
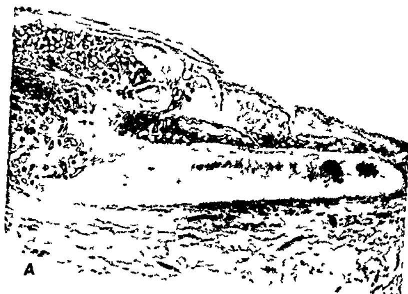


Fig 143—Carcinoid type of adenoma A low power B high power

formed which is constricted as though by a ligature at the point of origin of the tumor, i e in the wall of the bronchus The intrapulmonary component of the tumor often attains the size of a hen's egg while the intraluminal component (probably because of space limitation) rarely exceeds the size of the bronchial lumen Some carcinoid tumors expand along the wall of the bronchus and produce a so called "intramural adenoma"

In its early stages (Fig 142) the tumor appears as a sessile mammillary projection above the surface of the bronchial mucous membrane It does not erode the mucosa as cancer does, but lifts it and remains

covered by it indefinitely The cells of the mucosa usually undergo a metaplastic change and the bronchial lining appears as a stratified squamous epithelium



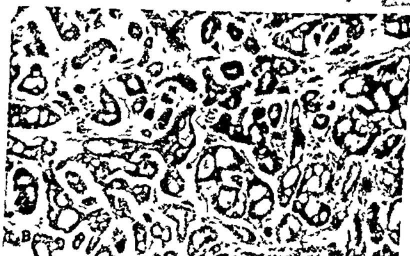


FIG 144.—Cylindroid type of bronchial adenoma A cut surface of the tumor showing an intact bronchial lining B the histology of the cylindroma

As the tumor grows its constriction at the base remains virtually unchanged while the two components i e the intraluminal and the intrapulmonary slowly but steadily increase in size Unopposed by the environment the intrapulmonary tumor takes on a round or slightly

oval shape The intrabronchial tumor, molded by the bronchial tube, assumes a pyriform shape that gradually becomes pedunculated hanging from the constricted attachment like the clapper of a bell (Fig 150) It usually projects upward toward the trachea because of the expulsive effort of coughing. Ultimately it fills the bronchial lumen and if left *in situ* will dilate the bronchial wall and produce a sacculation (ectasia)

When viewed with the bronchoscope it looks like an inflamed, bulging eardrum crossed by numerous tiny blood vessels In color it is gray, pink or grayish pink Although it shows no erosions it does show oozing which is probably due to inadvertent trauma caused by the instrument or by stretching

Dissimilarities —In addition to their histological differences the 2 types vary in many other respects These may be summarized as follows

1 The bronchus invariably is the site of origin of the carcinoid type, while the cylindroid type may arise in the trachea as well

2. The carcinoid type arises either in the main stem or in a lobar bronchus in about 95 per cent of cases while the cylindroid type arises in these sites in only 65 per cent It has been stated that the upper lobes are rarely the seat of either variety (Reid reported 2 cases as did Enterline and Schoenberg)

3 The carcinoid type has a slight predilection for the female sex while the cylindroid type has no sex predilection

4 The average age of the patients at the onset of symptoms is about 35 in the carcinoid type and about 40 in the cylindroma type

5 The carcinoid type to all appearances is a benign neoplasm It has not been observed to break into the circulation has rarely metastasized to distant organs and has rarely recurred after removal It has not been affected by radiation and has not been known to cause constitutional symptoms or death It is surrounded by a capsule and like other benign tumors is expansive but not invasive

6 The cylindroma type has revealed malignant features Reid found metastases in 14 out of 50 cases studied In 6 cases the neoplasm had recurred and in 7 cases death was caused by the spread of the tumor Enterline and Schoenberg found metastases in 32 per cent of their cases and recurrences 7 times more often than in the carcinoid type They also noted that the cylindroma type caused death 7 times more often than the carcinoid type In 87 cases culled from the literature by McBurney and his associates 46 showed metastases in the regional lymph nodes in the other 41 cases the metastases were found in the visceral organs chiefly in the liver In 14 cases the adjacent organs were involved by direct extension However the metastases occurred late in the course of the disease and were not in evidence for 5 or more years after the appearance of symptoms Moreover in 7 fatal cases the average duration of life was over 9 years dating from the time of the onset of symptoms

Patients survived for several years after the appearance of dista metastases

7 Unlike the carcinoid type, the cylindroid type is considered neoplasm of low grade malignancy. It has been observed 10 times le often than the carcinoid type—an incidence of about 1 to 100 of benign bronchial neoplasms

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Like other benign, as well as malignant tumors, bronchial adenom passes through a "silent" (preclinical) stage Some adenomas, partic larly those of the peripheral type, remain asymptomatic "from the cradl to the grave" In 2 of my own cases, adenomas of considerable size which were discovered at autopsy, did not yield symptoms at any time However, the majority of them begin to manifest themselves long befor the development of irreversible pulmonary changes It is of the utmos importance to diagnose and to eradicate the tumor before complication set in In the carcinoid type the average age at the onset of symptom is about 35, in the cylindroma type, it is about 40

Clinical Phases—It is well to divide the clinical course into three phases (1) preobstructive, (2) intermittently obstructive, and (3) permanently obstructive (Table 18)

Table 18. Salient Diagnostic Features

			Clinical Manifestations		
Age	*Sex*	*Site*	*First Phase Preobstructive*	*Second Phase Obstructive*	*Third Phase Constantly Obstructive*
80 to 85% under 40	55% in the female	About 60% on the right side	Dry or moderately productive cough, occasional streaking of sputum with blood intermittent respiratory infections occasional wheeze	Cough hemoptysis, wheeze in chest, recurrent "colds," pneumonitis with pyrexia, pain in chest	Atelectasis of lung distal to obstruction, bronchiectasis putrid abscess, empyema, constitutional symptoms

Of the two components of the adenoma, i e, the int and the intrabronchial, only the latter manifests itself clin s probably occur at the st e disease, due, not adenoma *per se*, as to th the bronchus that.

new growth They consist primarily of a cough induced by the alien stratified squamous epithelium that replaces the normal lining of the bronchial mucosa Changes in the mucosa are invariably accompanied and possibly preceded by changes in the submucosa and the muscularis mucosa

Chevalier Jackson described the bronchi as a "living moving labyrinth of resilient tubes which change in diameter length and contour with respiration Changes in the structure of the bronchus lead to loss of its resiliency and impairment of its dynamics This causes the persistent tussive effort Cough is an incipient manifestation of the benign as well as the malignant tumor of the bronchus It is such a common symptom that it is usually disregarded or else it is treated with remedies that alleviate the symptom but not the cause

Since the bronchus is an inseparable part of the pulmonary parenchyma the "resilient tube" affection is invariably followed by an impairment of the respiratory and defensive* functions of the segment or lobe of the lung supplied by the diseased bronchus The lungs become a ready prey to infection Patients sporadically suffer from attacks of bronchopneumonitis ("recurrent pneumonitis) and while this is being treated symptomatically the undiscovered disease pursues its relentless course

Adenoma has been compared with an iceberg since only part of it is visible on the surface and like an iceberg its advance is very slow The chronic nature of the disease is aggravated by the multiplicity of the recurrent episodes of pulmonary infection which ultimately leads to indurative pneumonitis bronchiectasis putrid abscess and empyema

Hemoptysis—Hemoptysis which occurs abruptly and often copiously is another manifestation of the preobstructive phase of the bronchial adenoma Formerly this symptom was attributed to tuberculosis and patients were referred to tuberculosis sanatoria Cases 12 and 13 are illustrative In carcinoma the bleeding which is of parenchymal and not bronchial origin is rarely abundant Usually a blood streaked sputum is found but frank hemoptysis is rare In adenoma the bleeding may reach a dangerous point at times Fatalities caused by profuse hemorrhage have been observed during the performance of bronchoscopic examinations

Wheeze—A wheezing sound heard in one side of the thorax while the patient's mouth is open is due to the passage of the current of respiratory air through a narrow channel moist enough to cause bubbling (Jackson) The sound is an unmistakable sign of almost complete obstruction The sound disappears when the obstruction becomes complete Wheezing is heard in virtually every progressively obstructive disease of the bronchopulmonary tree and is indeed a cardinal sign of partial obstruction

*Fried B M The lungs and the macrophage system, Arch Path 17 76 1934

in bronchial adenoma When a patient relates that he has become aware of a wheezing sound in his chest, it is well to remember Jackson's dictum that "not all is asthma that wheezes"

Pain in Chest—Patients with bronchial adenoma often complain of pain in the chest The pain usually accompanies the infection of the lung (pneumonitis) and of the pleura

The enumerated signs and symptoms, whether combined or separate, should prompt the physician to search for an intrabronchial lesion A correct diagnosis is usually attainable by the use of the laboratory tests to be described later on

Age—No age group is immune to the tumor, but the highest incidence has been observed in persons between the ages of 30 and 40 The carcinoid type of adenoma has also been found in children and in young adults *Adenoma is rarely seen at the age period when carcinoma occurs* most frequently

Sex—Cancer of the bronchus occurs in an approximate 90 per cent incidence in men, and in only about a 10 per cent incidence in women In adenoma the difference between the sexes is very slight, *i e*, 45 per cent incidence in men, and 55 per cent incidence in women The age and sex incidence of the carcinoid type seems to support the belief that carcinoma and adenoma of the bronchi are unrelated neoplasms

Site—As stated above, the carcinoid type originates in the main stem or in a lobar bronchus in 95 per cent of cases In the remaining 5 per cent, the neoplasm arises in a small bronchiole at the periphery of the lung, *hence the term "peripheral adenoma" Unlike adenoma, peripheral* carcinoma is observed in about 20 per cent of cases The cylindroma type arises in the main bronchi in about 65 per cent of cases The upper lobes are very rarely the sites of origin of either neoplasm The right side is the seat of the tumor in about 60 per cent of cases

ROENTGENOGRAPHY

At the outset, it is well to emphasize that when a persistent cough is present, and there are recurring episodes of "colds" (pneumonitis), a roentgenological examination of the chest is mandatory, and the antero-*posterior and the lateral views* should be studied Because the adenoma, in most instances, is bidirectional, *i e*, intrabronchial and intrapulmonary, the latter will be promptly discovered As a rule, the dense shadow is of variable size It is central or hilar in position, is well defined, and occasionally shows calcium deposits Tomographic studies are helpful in the determination of the depth of the shadow The difficulties encountered in arriving at a correct diagnosis of a solitary "coin" lesion, found in the midst of the normal pulmonary parenchyma, was pointed out in Chapter 2 In some cases the roentgenologist is at a loss,

and at other times he interprets the shadow as cancer. There is indeed not one feature that is singularly characteristic of the benign adenoma.

The x ray examination should therefore be followed by a bronchoscopic investigation.

BRONCHOSCOPY

On bronchoscopic examination the appearance of the lesion will depend upon the phase of the disease, e.g. preobstructive, sporadically obstructive (semi or partially obstructive) and fully obstructive. The bronchoscopic view of the benign neoplasm is characteristic and can hardly ever be confused with that of a carcinoma. As stated above the adenoma is roughly round or globoid in shape, is often pedunculated and is covered by a smooth capsule crossed by blood vessels running in different directions. Usually it is sharply outlined and bleeds readily. The condition of the bronchial wall adjacent to the tumor and the condition of the carina are of equal importance. Unlike carcinoma, the bronchial tube in adenoma retains most of its resiliency and the cartilaginous rings that are usually effaced in carcinoma are conspicuous in adenoma. The carina retains its pointed shape unless the mediastinal lymph nodes have been affected by an inflammatory disease (tuberculosis).

The bronchoscopist is, moreover, in a position to determine the exact location of the tumor as well as the state of the lung supplied by the affected bronchus. With the introduction of telescopic lenses the field of vision that can be reached by the bronchoscope has been widened and tumors hitherto considered to be outside the line of vision are now accessible to inspection.

It is imperative that tissue be removed for histological examination and that the bronchial secretions be collected for cytological studies.

The bronchoscopist serves yet another purpose. In cases where there is an obstruction of the bronchial lumen, whether by the tumor or by a mucous plug, the removal of the obstructing matter opens the lumen and brings about reaeration of the lung.

Illustrative Cases

Case 12 (Figs 143 and 145).—This case (a woman 30 years of age) *is a classical example of the carcinoid type*.

1 The tumor was made up of two components—intrabronchial and intrapulmonary.

2 The symptoms consisted of cough, hemoptyses and sporadic colds ("recurrent pneumonitis").

3 Therapy applied to the intrabronchial segment of the growth for seven consecutive years failed to eradicate the disease but cure was accomplished by a lobectomy.



FIG 145—(Case 12) *A*, adenoma embedded in the pulmonary parenchyma, *B*, cut surface of the adenoma showing an area of necrosis



FIG 146—(Case 13) A wedge shaped density in the right lung due to atelectasis caused by obstruction of the bronchial lumen

4 It is typical too by its location mode of growth and structure

Case 13 (Fig 146)—This case (a woman 27 years of age) is another example of adenoma diagnosed by a bronchoscopic biopsy Histologically it was an adenoma of the carcinoid type and clinically it demonstrated the obstructive phase It was typical by its onset with cough and bloody expectoration and by the protracted duration of the illness Here too the diagnosis of tuberculosis was entertained until the bronchoscopic examination revealed an obstructive benign neoplasm The bronchus showed a quasi complete obstruction which led to atelectasis

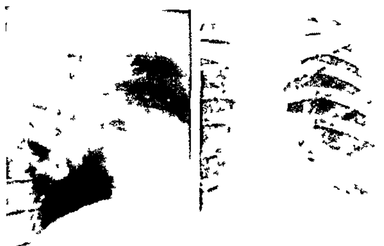


Fig 147 —(Case 14) Carcinoid adenoma in the left lower lobe

of the right upper lobe But because of the sporadic bronchoscopic treatment the patient had escaped the dangerous sequel of bronchostenosis Unlike the patient in the preceding case in whom the diagnosis of tuberculosis was entertained for a relatively short time this patient was treated as tuberculous for a period of 2 years

Case 14 (Fig 147)—A critical analysis of the history of a male patient 31 years of age suggested that the symptoms attributable to the respiratory organs preceded the discovery of the tumor by only a few weeks They were mild and did not suggest the presence of a bronchopulmonary neoplasm Therefore the roentgenological finding of a neoplasm of the lung was a surprise The nature of the tumor i e whether it was benign or malignant primary or metastatic—and finally whether it was



FIG 150—(Case 17) *A* a pedunculated ovoid endobronchial adenoma projecting upwards *B* the acinar structure of the carcinoid adenoma

Fig. 151.—(Case 18) A well circumscribed, roughly round tumor in the region of the right middle and lower lobes. The roentgenological appearance of the cut surface of the lung and tumor is shown in *B*. The tumor is almost entirely calcified.

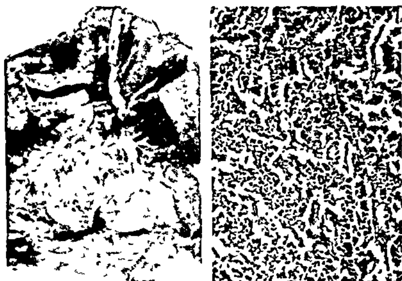


Fig. 152 (Case 15) The cut surface of the encapsulated adenoma. The histological structure of the tumor.

[illegible] She had not been examined roentgenologically un [illegible] and when a roentgen examination of her chest w performed by her physician at the onset of the illness it w reported as [illegible] should have been accept with [illegible] as a small tumor in the lu [illegible] and craftsmansh [illegible] in order to understa [illegible] solved the problem.



not by the tumor, but by rheumatic carditis At autopsy the growth did not appear to have changed in size or shape since the



Fig 154—(Case 19) A tumor at the base of the right upper lobe The roentgenological appearance of the tumor is indicated by arrow

[illegible]

by the bronchus which was affected by the tumor showed an indurative pneumonitis

8 years She had not been examined roentgenologically until 1955, and when a fluoroscopic examination of her chest was performed by her physician at the onset of the illness, it was reported as negative This report should have been accepted with reservation The discovery of a small tumor in the lung with the fluoroscope requires experience and craftsmanship The patient was studied with diligence in order to understand the nature of the tumor A thoracotomy solved the problem



Fig 153—(Case 18) A, bone formation within the tumor Tumor is seen above the bone spicule and myelopoiesis below the bone spicule B an area of hyalinization and necrosis

growth did not appear to have changed in size or shape since the



Fig. 151.—(Case 19) A, tumor at the base of the left upper lobe. The roentgenological appearance of the tumor is indicated by arrow.

time the bronchoscopic examination was made 3 years before. The patient had been suffering from an intense cough and from recurrent episodes of pulmonary infections. The lung supplied by the bronchus which was affected by the tumor showed an indurative pneumonitis.

Case 18 (Figs 151, 152 and 153)—The benign tumor in a woman 62 years of age, originated in the wall of a large bronchus which it obliterated. *Within the lung it formed a sizeable mass* that compressed adjacent structures but did not invade them. *It grew slowly* and became extensively ossified and hyalinized. *There were foci of extramedullary myelopoiesis*

This case is another *example of the* benign clinical course and pathological pleomorphism of bronchial adenoma.

Case 19 (Figs 154 and 155)—The adenoma in this case was

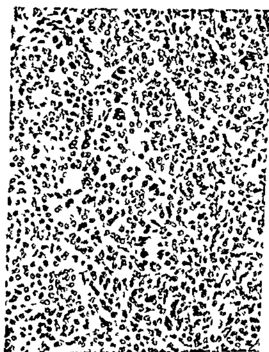


FIG 155—(Case 19) The histological appearance of the tumor

accidentally discovered in a woman, 64 years of age, while she had been under medical care for a cardiac disease. Apparently the tumor had caused no symptoms, or the symptoms were mild and overshadowed by the cardiac disease to which she succumbed. *At autopsy the adenoma* was found to be well encapsulated and the lung around it was normal

This case is another example of an asymptomatic, or "silent," adenoma of the bronchus

TREATMENT

When the tumor is confined solely to the bronchus, bronchoscopic *therapy with radium, forceps,* electrocoagulation or aspiration is sufficient

to cure the disease However, since in most instances the growth is also found in the lung, therapy should be directed toward the removal of both components of the neoplasm, *i e*, the intrabronchial and the intrapulmonary To treat the intrabronchial component alone, as has been practiced in the past is like trying to ram only the visible part of an iceberg The aim is to eradicate the hourglass like tumor *in toto* while sparing the normal pulmonary tissue The procedure to be used whether pneumonectomy lobectomy, or bronchostomy depends entirely upon the size and localization of the tumor, and particularly on the condition of the lung, *i e*, whether or not there are reversible changes

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Chapter 14

Rare Tumors

The study of diseases of the lungs took a new turn with the widespread use of x rays, which made physicians aware of tumors that had not previously been observed or recorded. While rare tumors had long been identified in other parts of the body, those of the lungs are still comparatively new. As a rule, they are benign, noninvasive and nonmetastasizing. Their clinical significance lies in their frequent location in the bronchial wall, from where they advance toward the bronchial lumen and the pulmonary parenchyma to induce an array of symptoms. Some of them lie dormant within the pulmonary parenchyma for years and are detected either at a routine x-ray examination of the lungs or because of a complication which they have induced. Outwardly many of them resemble malignant tumors. In this chapter the most commonly encountered of these tumors will be briefly discussed.

SARCOMA

Sarcoma of the lung may arise in the connective tissue or in the lymphoid tissue. Sarcomas of connective tissue origin are divided into (1) parenchymal sarcomas, which arise in the lung proper, and (2) bronchial sarcomas, which arise in the wall of the bronchus.

Parenchymal Sarcoma.—The parenchymal or peripheral sarcoma—which is a solitary growth—usually is firm in consistency and is surrounded by a dense fibrous capsule. It is composed of spindle cells that resemble the oat cells in bronchogenic carcinoma. It grows slowly and is of low grade malignancy. In most instances a cure is effected by its removal. Of 19 cases of pulmonary sarcoma reviewed by Iverson, the tumor recurred after removal in only 6. The possibility of a late recurrence or of an ultimate appearance of metastases to the bone and the viscera, although rare, should be borne in mind (Fig. 156).

Bronchial Sarcoma.—This neoplasm (observed in persons of middle and past middle age) is essentially an endobronchial polypoid growth composed of plump oval cells, larger in size than those observed in the parenchymal type. Bronchial sarcoma is still less malignant than parenchymal sarcoma. In one reported case a rapidly growing fibrosarcoma of the bronchus was expectorated without leaving a trace in the bronchus or elsewhere in the body. Up to 1951 only 8 cases had been reported. While the parenchymal sarcoma remains asymptomatic for an indefinite



Fig 156—Sarcoma of the lung

period of time the bronchial type by virtue of its location ultimately produces symptoms which are caused by bronchial obstruction The tumor can be seen with the bronchoscope but because of the degenerative state in which the growth is usually found the removed tissue is rarely suitable for diagnostic purposes

CARCINOSARCOMA

Carcinosarcoma is a neoplasm that is made up of two components (1) a nonkeratinizing squamous cell cancer and (2) a connective tissue cell fibrosarcoma Some pathologists regard the tumor as a symbiosis of two independent neoplasms which have merely collided others consider it to be a single growth in which the parenchyma is made up of malignant epithelial cells while the stroma is sarcomatous (Fig 157)

Be that as it may the tumor is an endobronchial growth which repeatedly has been found to occupy almost the entire lumen of the

bronchus, having spread intraluminally in a finger-like manner in the direction of the bronchial branches. It has also been found to break through the bronchial wall and penetrate the pulmonary parenchyma, thus forming an hourglass-like shape with a constriction similar to that seen in a bronchial adenoma.

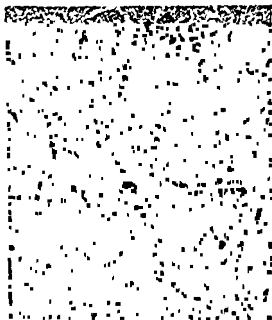


Fig. 157.—Carcinosarcoma. Tumor removed from the lung (lobectomy) in 1953. Intestinal resection for metastasis in 1954. Patient alive in December, 1957.

Carcinosarcoma is a moderately malignant, slow-growing tumor. Of 2 cases treated by pneumonectomy, 1 patient survived for 6 years, the other for 3 years. However, on occasion, the tumor has been observed to recur several years after removal. In some reports, it was termed a "pedunculated intrabronchial polyp" with a limited capacity for invasion.

This neoplasm is found in persons of cancer age. Its symptoms, due to bronchial obstruction and to the ensuing pneumonitis, consist of cough, expectoration, fever, malaise, and loss of weight. The diagnosis is made on the basis of a bronchoscopic biopsy.

LYMPHOSARCOMA

Lymphosarcoma is a tumor which usually arises in organs that are made up essentially of lymphoid tissue, as, for example, the lymph nodes

The tumor metastasizes to different visceral organs including the lungs The incidence of pulmonary metastases in lymphomatoid disease is discussed in Chapter 16 However cases are on record in which a lymphosarcoma happened to arise primarily in the lungs (Fig 158) It may be well to point out that the normal lung contains lymphoid tissue which is scattered in nests around the bronchi and the blood vessels

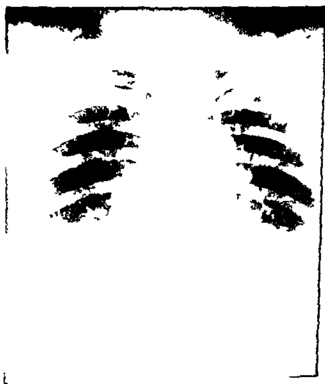


Fig 158 —Solitary benign lymphoma of right lung

A primary lymphosarcoma of the lung consists of a solitary firm mass of small or large lymphoid cells which infiltrate the contiguous pulmonary tissue The size of the lymphoma varies from one case to another but it has never been observed to be larger than an orange Pekelis reported a case with metastases to the ribs and the liver The new growth visible with the roentgen rays is a round or oval area of density with either clear or hazy borders No calcification is present In the case reported by Spatt and Grayzel the x ray picture suggested an encapsulated pleurisy

The patients complaints are protean In the case reported by Sarokhan and Morrison the complaint was chronic cough In Spatt and Grayzel s

case it was cough, bloody sputum, an occasional gnawing pain in the chest, and loss of weight. In the case reported by Weissman and Christie it was a persistent cough of 1 years duration, weakness, dyspnea, and a loss of 16 pounds within a period of 6 months.

Bronchoscopy and cytological studies are not revealing. The cases hitherto reported in the literature were diagnosed either through a thoracotomy or at autopsy.

The treatment consists of the surgical removal of the lymphoma followed by radiotherapy. It is very likely that radiation therapy alone is sufficient to yield a radical cure.

PLASMACYTOMA

Plasma cell tumors usually originate in the bone marrow. However, plasmacytomas may originate in organs other than the bone marrow, mainly in the upper respiratory tract. In the lung and in the mediastinum the plasmacytoma is usually seen as a solitary growth, round or oval in shape and well demarcated. It has rarely exceeded the size of a golf ball and is made up of typical plasma cells.

According to most observers, plasma cells descend from undifferentiated mesenchymal cells, although histologists trace their origin to lymphocytes alone. They also find analogies between plasmacytomas and lymphocytomas, i.e., in radiosensitivity.

It is difficult to differentiate between a plasma-cell tumor and a plasma-cell granuloma. Hellwig found that from the prognostic point of view the localization and the microscopic appearance of the growth provide better criteria than the histological structure. Extramedullary plasmacytomas have been observed to produce changes in the electrolytes of the blood quasi similar to multiple myelomas. Tumors of this type which begin as benign localized lesions may remain so for many years, but ultimately many of them become generalized.

As a rule, the pulmonary plasmacytoma produces no symptoms. Childress and Adie reported a case of a man 27 years of age who complained of a dry hacking cough and of a loss in weight. His sputum was blood streaked. The physical examination proved negative, but the roentgenological study revealed a dense, well circumscribed, elliptical mass in the area of the right middle lobe. The mass measured 4 cm in diameter, extended through the interlobar fissure, and involved a portion of the upper lobe. The removed plasmacytoma measured 4 × 3 × 3 cm. It was well demarcated but not encapsulated.

In another case reported by the same authors the plasmacytoma measured 7 cm in diameter. It had been located in the posterior mediastinum. On removal the tumor was found to be spindle shaped and measured 6.5 × 3.5 × 3.5 cm. It was surrounded by a capsule and was

made up of mature plasma cells that grew in a vascularized stroma Of clinical interest is the fact that like lymphocytomas plasmacytomas are radiosensitive

LIPOMA

Lipoma of the lung and bronchi is structurally similar to lipomas found in other parts of the body The tumor originates from the fat cells normally present in the mediastinal space and in the wall of those bronchi which contain cartilaginous plates Whether some of the lipomas (possibly all) are congenital has not been established

Mediastinal lipomas are divided into (1) those lying entirely within the thoracic cavity and (2) those lying partly within and partly without the mediastinal space producing hourglass shaped tumors The external component of the lipoma results from the squeezing out of a part of the intrathoracic mass through an intercostal space or through a defect in the sternum A bulge covered by the skin and the subcutaneous tissues is thus formed Cases have been reported where the intra thoracic lipoma either pierced the diaphragm or grew into the pleural cavity some lipomas advanced toward the neck

Keeley and Vana reviewed 82 cases reported in the literature from 1940 to 1955 Of this number 46 were mediastinal lipomas confined to the anterior mediastinum 18 were of the hourglass variety 7 were cervicomediastinal and 11 were transmural

Endobronchial lipomas as stated above originate from the adipose tissue normally present in the bronchial wall Similar to adenomas they tend to advance in two directions toward the pulmonary parenchyma and toward the bronchial lumen or in one direction toward the bronchial lumen only The early phases of the endobronchial tumor have never been observed but it is believed they follow the course of other types of benign endobronchial neoplasms In the 14 cases reviewed by Ochsner and his associates the tumors were found to be located in large sized bronchi They were solitary oval in shape firm in consistency and covered by the bronchial mucosa

The following case of a mediastinal lipoma came under observation at the Morrisania City Hospital The patient a woman 19 years of age was admitted to the obstetrical service for the normal delivery of a child A routine x ray examination of the chest revealed an area of density merging with the right border of the heart It appeared to be conical in shape with its base lying flat on the diaphragm (Fig 159) The patient s past history was irrelevant except for the fact that 5 years earlier at the age of 14 an identical picture had been obtained at a routine x ray examination The conical shape had been interpreted as being due to enlargement of the heart

Lateral views as well as angiography failed to show a connection

between the heart and the dense area. The process appeared to be neoplastic (Figs. 160 A, B and C).

Four months after delivery the woman was readmitted to the hospital. A thoracotomy was performed and an oval lobulated encapsulated mass was removed from the anterior mediastinum. It had been covered by the pleura and laid adjacent to the heart. It weighed 750 gm. and measured 20 × 12 × 10 cm. Microscopically the mass consisted of normal adipose tissue with a few normal thymic elements here and elsewhere.



Fig. 159.—Lipoma (?Thymolipoma) of the mediastinum, posteroanterior and lateral views.

Similar cases were reported by Yater and Liddine, as well as by Gottlieb, Bier and Jordan. The case of Gottlieb and his associates concerned a man 30 years of age who was hospitalized in order to determine the cause of an alleged cardiac enlargement. The man was in perfect health but the roentgenological examination revealed a shadow similar to the picture shown in Figure 159 which was interpreted as demonstrating hypertrophy of the heart. The nature of the shadow was ultimately determined after a painstaking clinical and laboratory investigation. In the case presented here, angiography and lateral view films immediately pointed out the neoplastic character of the process. Gottlieb and his associates, in their article, quote Sosman and Levine who had demonstrated a similar case at a clinical meeting during the Annual Congress of the American College of Physicians in Boston in 1949. In Sosman and Levine's case, too, the original diagnosis was cardiac hypertrophy.

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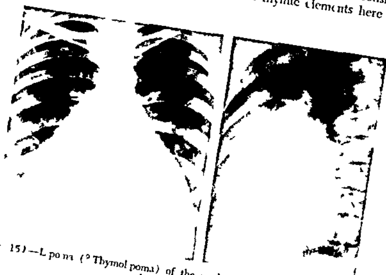


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Clinical Manifestations—The symptoms caused by the mediastinal and the endobronchial lipomas are different and therefore will be discussed separately

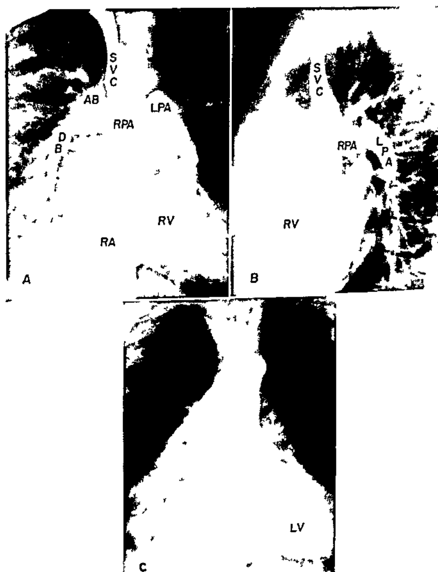


Fig 160—Angiograms *A* *B* and *C* show the abnormality to be due to a new growth and not to cardiac hypertrophy or to pericardial effusion SVC supe ior vena cava LPA left p lmonary artery RPA right pulmonary artery AB iscend ng branch of the pulmonary artery DB descending branch of the pulmo- nary artery RA right atri m RV right ventricle LPA left pulmonary artery In C the opacification (fill ng) of the left ventricle reaches the cardiac silhouette thereby differentiating it from a pericardial effusion

In the mediastinal lipoma symptoms depend chiefly upon the size of the tumor and its location. Small lipomas usually are asymptomatic while the large tumors compress the neighboring structures and cause pain in the chest, exertional dyspnea, cough and a sensation of heaviness in the thoracic cavity. Dysphagia, epigastric pain and edema of the upper extremities have been the chief complaints in some cases. Reviewing 38 cases of intrathoracic lipomas McCorkle found that in 16 instances the patients complained of dyspnea, in 11 they complained of pain in the chest and in 7 of cough. 2 patients suffered from hemoptysis and 2 from hoarseness. Eight of the patients mentioned above showed cyanosis and 1 suffered from anginal attacks.

The endobronchial lipoma has not been observed in the preobstructive cases. Its clinical course, no doubt, is an imitation of the picture of endobronchial adenoma discussed in detail in Chapter 13. It is much less prone to the bleeding that is so characteristic of the adenoma. It affects the lungs in ways similar to the adenoma causing an obstructive pneumonitis, bronchiectasis and other types of putrid processes which are grave and irreversible.

They grow very slowly, as evidenced by the colossal size some of them have attained. Of 11 cases reviewed by Yater and Liddane the largest lipoma weighed 17 pounds and 6 ounces and the smallest was twice the size of an egg. In Watson and Urban's case the tumor measured 30 × 23 × 22 cm and weighed 16 pounds and 8 ounces. In Gottlieb's case it measured 18 × 11 × 8 cm. In my own case (mentioned above) the lipoma weighed 25 ounces (750 gm) and measured 20 × 12 × 10 cm.

Diagnosis.—Bronchoscopic, roentgenological and angiographic examination will reveal the nature of the lesion and its precise location.

On roentgenological examination the tumor is seen as a somewhat lobulated area of density. Heuer and Andrus made a diagnosis of a mediastinal lipoma on the basis of a roentgenogram which showed a diminished radiolucency at the periphery of the tumor. This phenomenon suggested to them that the tumor was composed of fat which is more readily penetrable by the x rays than the compact tissue of other mediastinal tumors. The preoperative diagnosis of a lipoma made by Crutcher and Plott was based upon the same principle.

Treatment.—Uncomplicated cases of endobronchial lipoma are treated successfully with the bronchoscope, i.e., by fulguration. When bronchial obstruction occurs and is complicated by a putrid process in the lung thoracotomy with the removal of the tumor as well as the affected portion of the lung is imperative. Intrathoracic lipomas are treated surgically.

LEIOMYOMA

The histological structure of a leiomyoma that is found in the lung is an exact counterpart of that of a leiomyoma found in the uterus. In the

few cases that had been reported in the past, diagnoses had been made on autopsy findings only, but in recent years diagnoses have been arrived at *intra vitam*

In an analysis of 4 cases of benign leiomyomas and 3 cases of malignant leiomyosarcomas, Sherman and Malone found that, grossly, the benign variety could not be distinguished from the malignant type because both are encapsulated However, the malignant leiomyosarcoma could not be shelled out from the capsule as readily as the benign leiomyoma Both types were oval and firm and caused no reaction, either in the surrounding tissue, the mediastinum, or the pleura They were solitary and did not metastasize On x ray examination they were well demarcated and could easily be confused with a solitary metastatic nodule, a tuberculoma, a cyst, an adenoma, or a bronchiogenic carcinoma In 1 case, the tumor, which measured 1 cm in diameter, was confined to the bronchial lumen alone, while in the remaining 6 cases it was found in the pulmonary parenchyma

That leiomyosarcoma of the lung is as malignant as its counterpart in the uterus is demonstrated in the case reported by Tocker, DeHaan, and Stofer It concerned a male, 19 years of age, who complained of weakness, anorexia, and loss of 35 pounds in weight in 4 months

Roentgenological examination revealed a round tumor mass with small nodular extensions in the left lower lobe behind the heart

At pneumonectomy a tumor was found which measured 11 cm in the maximum diameter and weighed 300 gm It was not encapsulated and was easily separated from the surrounding tissue, leaving a shallow, rugged depression The microscopic diagnosis of a leiomyosarcoma was made No metastases were found

Four months after the operation 2 subcutaneous nodules appeared, which in time grew and became ulcerated A biopsy showed them to be metastatic from the pulmonary leiomyosarcoma Six months later metastases were discovered in the remaining lung About 1 year after the onset of symptoms the man died

At the autopsy a tumor was found in the left pleural cavity, growing through the intercostal space, in the right lung, and in the abdominal lymph nodes

Summary —Leiomyomas are found in patients whose ages range from 8 to 63, and leiomyosarcomas are found in patients from the ages of 4 to 83 Leiomyoma is found more often than leiomyosarcoma When localized leiomyosarcomas can not be eradicated surgically, radiotherapy affords palliation

Pierce, Alznauer, and Rolle, in a report of a case of leiomyoma of the lung, pointed out that the possibility of a pulmonary lesion being a metastasis from an extrapulmonary leiomyosarcoma should always be considered

MYOBLASTOMA

Although this type of tumor found outside the lungs has been extensively studied no conclusion concerning its histogenesis has been arrived at. Indeed some doubt still exists as to whether it is a neoplasm or a granuloma. The tumor (which we believe it to be) is composed of myoblasts which, embryologically, are precursors of the striated muscle. Some authors have stated that it originates from pluripotential mesenchymal cells and others are of the opinion that the structure is merely a degenerative lesion of the striated muscle. It is found in various parts of the body, e.g., the skin, the lips, the tongue, the lacrymal sac, the breasts, the thymus, the vulva, the trachea, the vocal cords and the bronchi. It appears as a small lump from .5 to 2 cm in size. It has no capsule and grows very slowly. As Murphy and his associates have stated, patients consult the physician for fear of cancer and not because of any disturbances due to the tumor, since it causes none.

The neoplasm is classified into (1) the uniform type which consists of sheets and cords of large granular cells, i.e., myoblasts and (2) the pleomorphic type which is composed of myoblasts and of a spindle cell stroma with scattered giant cells. Many subvarieties have been observed. Malignant myoblastomas have been reported by both Khanolkar and Ackerman.

It is well to state that local invasiveness is characteristic of many granular-cell myoblastomas which are benign in every respect. The majority of cases were discovered in patients in the third, fourth and fifth decades of life.

Several cases of granular cell myoblastoma have been found in the lungs and bronchi. Lowbeer reported a characteristic case. It concerned a woman 24 years old who complained of a productive cough and of wheezing sounds in the chest. On roentgenological examination there was atelectasis of the left lung and on bronchoscopic examination a tumor that was obstructing the left main bronchus. The resected lung showed the presence of a polypoid tumor in the lumen of the left main bronchus; its origin was traced to the bronchial wall. The tumor was identified as a granular cell myoblastoma.

The symptoms caused by this tumor were identical with those caused by other polypoid endobronchial neoplasms which obstruct the lumen of the bronchus.

HAMARTOMA

The term "hamartoma"* was originally applied to benign neoplasms found in the liver or spleen. Composed of normal tissues of the organ

*In Greek hamartoma means to fail or err.

in which they arise they are arranged in a haphazard manner and sho various degrees of differentiation of the tissue

It was pointed out by Goldsworthy that some cases reported as chondromas of the lungs were hamartomas Jaeger differed from this only by calling attention to the multiple and erratically arranged components such as cartilage connective tissue glandular lymphoid and vascular elements and adipose and osseous tissues of hamartomas

Hamartomas occur within the pulmonary parenchyma or as intrabronchial polypoid growths The intraparenchymal tumor usually is round or egg shaped lobulated firm encapsulated and loosely attached to the surrounding tissue from which it can be separated with relative ease On its cut surface it is grayish white with a bluish tinge The growth often shows areas of calcification and ossification similar to that of other benign pulmonary neoplasms such as thymomas terato dermoids o granulomas (*e g* tuberculomas) It contains a great deal of ad pose tissue a condition which is also observed in adenoma of the bronchus

Location —The intrapulmonary hamartoma usually is located in the periphery of the lung adjacent to the pleura and in the vicinity of either the interlobar fissure the hilus or the diaphragmatic surface In some instances it has been found suspended by a pedicle to the pleura and protruding into the pleural cavity There is no connection between the growth and the bronchial cartilage

Histology —Microscopically hamartomas are made up of connect ve tissue which shows mucoid degeneration They also contain clefts that are lined by cuboidal or columnar epithelium adipose tissue smooth muscle blood spaces lymphocytes bone and calcium Hamartoma is a benign slow growing tumor that is surrounded by a dense connective tissue capsule which varies in thickness

Age—Sex—Site —This type of tumor has been found in persons of various ages Bayer observed 1 in a woman of 81 Adams found 1 in a boy of 9 and Jones described such a tumor in a newborn infant Jones s case concerned a baby girl who had been delivered on the twenty eighth week of pregnancy and died 4 hours after birth The left lung was atelectatic while the partially aerated right lung weighed 50 gm and contained a spherical circumscribed nonencapsulated mass 3 5 cm in diameter which occupied almost the entire upper lobe On its cut surface the mass was pink and firm with coarse whorls and interlaced bands of white fibrous tissue Microscopically it was made up of immature mesenchymal tissue fibrous tissue fetal fats cartilage and imperfectly formed bronchial structures

Hamartomas occur with greater frequency in the male Of 86 cases collected from the literature 67 occurred in the male and 19 in the female—a ratio of 3 to 1 They vary in size from a few millimeters to several centimeters In a case reported by Buss the tumor occupied

the entire pleural cavity while in the case of the infant reported by Jones the tumor measured 3 5 cm in diameter

It has occurred with greater frequency in the right lung Of 82 cases culled from the literature 51 hamartomas were on the right side and 31 on the left side The incidence as to lobe cannot be accurately stated because it has not been mentioned in many reported cases

Endobronchial Hamartoma —The microscopic and macroscopic appearances of the endobronchial tumor are identical with the intrapulmonary type In its early stages the growth protrudes into the lumen of the bronchus forming a mammillary protrusion on a broad base In its advanced stages it becomes sessile and begins to flap It is firm and avascular and will remain within the bronchial lumen for life unless removed Hamartomas have been observed to occlude the lumen of the bronchus completely

The endobronchial tumor is observed much less frequently than the intrapulmonary tumor Of 98 cases of chondrohamartoma reviewed by Postlethwaite and his associates only 13 were of the endobronchial variety However in recent years there has been a considerable increase in the number of reported cases

Manifestations —The intrapulmonary hamartoma remains asymptomatic until it either reaches a considerable size thereby causing compression of the lung and reduction of its respiratory capacity or when it encroaches on a vital structure When symptoms make their appearance they are quasi identical with the symptoms caused by an endobronchial adenoma

ARTERIOVENOUS FISTULA*

Pulmonary arteriovenous fistula is a condition where a shunt is present between several branches of the pulmonary artery and the corresponding radicles of the system of the pulmonary veins The vessels (the veins more so than the arteries) are markedly dilated forming a mass that resembles a primary or a metastatic cancer a tuberculoma or a cystic bronchiectasis

In about 60 per cent of cases the fistulas are multiple They are found mostly in the lower lobe of 1 or both lungs or in the right middle lobe Of 43 cases collected from the literature by Yater and his associates only 22 per cent were located in the upper lobes Both sexes are equally affected

On roentgenological examination the fistula is seen as an uneven mass of density (Fig 161A B C and D) it may vary in size from a small cherry to a hen's egg Sometimes it even replaces a whole lobe The borders of the area of density usually are well demarcated On fluoro-

*Also known as multiple pulmonary hemangiomas pulmonary arteriovenous aneurysms and cavernous hemangioma

in which they arise they are arranged in a haphazard manner and show various degrees of differentiation of the tissue

It was pointed out by Goldsworthy that some cases reported as chondromas of the lungs were hamartomas Jaeger differed from this only by calling attention to the multiple and erratically arranged components such as cartilage connective tissue glandular lymphoid and vascular elements and adipose and osseous tissues, of hamartomas.

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Manifestations —The intrapulmonary hamartoma remains asymptomatic until it either reaches a considerable size thereby causing compression of the lung and reduction of its respiratory capacity or when it encroaches on a vital structure When symptoms make their appearance they are quasi identical with the symptoms caused by an endobronchial adenoma

ARTERIOVENOUS FISTULA*

Pulmonary arteriovenous fistula is a condition where a shunt is present between several branches of the pulmonary artery and the corresponding radicles of the system of the pulmonary veins The vessels (the veins more so than the arteries) are markedly dilated forming a mass that resembles a primary or a metastatic cancer a tuberculoma or a cystic bronchiectasis

In about 60 per cent of cases the fistulas are multiple They are found mostly in the lower lobe of 1 or both lungs or in the right middle lobe Of 43 cases collected from the literature by Yater and his associates only 22 per cent were located in the upper lobes Both sexes are equally affected

On roentgenological examination the fistula is seen as an uneven mass of density (Fig 161A B C and D) it may vary in size from a small cherry to a hen s egg Sometimes it even replaces a whole lobe The borders of the area of density usually are well demarcated On fluoro

*Also known as multiple pulmonary hemangiomas pulmonary arteriovenous aneurysms and cavernous hemangioma

in which they arise, they are arranged in a haphazard manner and show various degrees of differentiation of the tissue

It was pointed out by Goldsworthy that some cases reported as chondromas of the lungs were hamartomas. Jaeger differed from this only by calling attention to the multiple and erratically arranged components such as cartilage, connective tissue, glandular, lymphoid and vascular elements and adipose and osseous tissues, of hamartomas

Hamartomas occur within the pulmonary parenchyma or as intrabronchial polypoid growths The intraparenchymal tumor usually is round or egg shaped, lobulated, firm, encapsulated, and loosely attached to the surrounding tissue from which it can be separated with relative ease On its cut surface it is grayish white with a bluish tinge The growth often shows areas of calcification and ossification similar to that of other benign pulmonary neoplasms such as thymomas, terato-dermoids or granulomas (*e g*, tuberculomas) It contains a great deal of adipose tissue, a condition which is also observed in adenoma of the bronchus

Location—The intrapulmonary hamartoma usually is located in the periphery of the lung, adjacent to the pleura and in the vicinity of either the interlobar fissure the hilus or the diaphragmatic surface In some instances it has been found suspended by a pedicle to the pleura and protruding into the pleural cavity There is no connection between the growth and the bronchial cartilage

Histology—Microscopically hamartomas are made up of connective tissue which shows mucoid degeneration They also contain clefts that are lined by cuboidal or columnar epithelium, adipose tissue smooth muscle, blood spaces lymphocytes, bone, and calcium Hamartoma is a benign, slow growing tumor that is surrounded by a dense, connective tissue capsule, which varies in thickness

Age–Sex–Site—This type of tumor has been found in persons of various ages Bayer observed 1 in a woman of 81 Adams found 1 in a boy of 9, and Jones described such a tumor in a newborn infant Jones's case concerned a baby girl who had been delivered on the twenty eighth week of pregnancy and died 4 hours after birth The left lung was atelectatic, while the partially aerated right lung weighed 50 gm and contained a spherical circumscribed, nonencapsulated mass, 3 5 cm in diameter, which occupied almost the entire upper lobe On its cut surface the mass was pink and firm with coarse whorls and interlaced bands of white fibrous tissue Microscopically it was made up of immature mesenchymal tissue, fibrous tissue, fetal fats, cartilage, and im[illegible]tly formed bronchial structures

[illegible] occur with greater frequency in the male Of 86 cases [illegible] from the literature 67 occurred in the male and 19 in the [illegible] ratio of 3 to 1 They vary in size from a few millimeters to [illegible] centimeters In a case reported by Buss, the tumor occupied



FIG 161.—Arteriovenous fistulas in the posterior segment of the right upper lobe (arrow) and in the *posterior basilar segment of* the left upper lobe (arrow). *A* shows two rounded opacities in the right upper lobe with afferent and efferent blood vessels leading to the hilus. The left lower lobe fistula is obscured by the heart and diaphragm. *B* lateral view shows the posterior location of the right upper lobe densities, also the round dense shadow at the left base. *C* frontal angiogram demonstrating the fistulas on the right and left sides. *D* lateral angiogram *showing segmental and posterior* location of the fistulas.



Fig 161

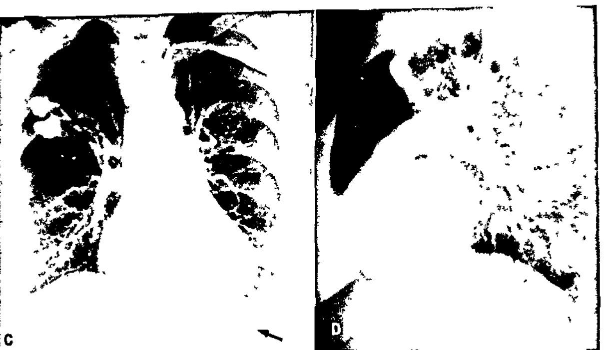


FIG. 161.—Arteriovenous fistulas in the posterior segment of the right upper lobe (arrow) and in the posterior basilar segment of the left upper lobe (arrow). *A* shows two rounded opacities in the right upper lobe with afferent and efferent blood vessels leading to the hilus. The left lower lobe fistula is obscured by the heart and diaphragm. *B*, lateral view shows the posterior location of the right upper lobe densities; also the round dense shadow at the left base. *C*, frontal angiogram demonstrating the fistulas on the right and left sides. *D*, lateral angiogram showing segmental and posterior location of the fistulas.

scopic examination the mass can be seen to pulsate, and in the laminograms one can discern two vascular shadows that connect the hilus with the mass The diagnosis is facilitated by the use of the Valsalva and Muller maneuvers In the Valsalva maneuver (forced expiration with the glottis closed) the intra alveolar pressure increases, and the pulmonary vascularity decreases In the Muller test (forced inspiration with the glottis closed) the intra alveolar pressure decreases, and the pulmonary vascularity increases, causing the angiomatous channels to distend with blood In about 50 per cent of cases the test is successful in demonstrating the vascular anomaly

Clinical Manifestations—Patients with an arteriovenous fistula may remain asymptomatic, but in most instances they suffer from serious disturbances Since there is a shunting of venous blood from the pulmonary artery to the pulmonary vein and left auricle, the blood which passes through the shunt bypasses the pulmonary capillaries and is inadequately oxygenated This induces cyanosis (which in some cases appears at an early age), dyspnea, polycythemia, and, occasionally, clubbing of the fingers The speech of the patients usually is thick, they suffer from headaches, dizziness, easy fatigability, epistaxis, and hemoptysis The bleeding may be so abundant as to be fatal (Rodes). Israel and Grosefield reported a case of a woman with a hereditary, hemorrhagic telangiectasia who had been treated for epistaxis for a period of 23 years At the age of 41 she developed hemoptysis, and when examined with the x rays, a pulmonary arteriovenous fistula was disclosed One year later she died of hemoptysis

On physical examination a continuous murmur is heard in the area of the fistula It is more intense on inspiration Occasionally, a thrill is felt In about 50 per cent of cases telangiectatic foci are found on the neck, the face, the lips, in the nasal mucosa, the mouth, and the gastro intestinal tract The blood pressure is not affected, and the spleen is not enlarged

Diagnosis—The pathognomonic signs are cyanosis, polycythemia, epistaxis, *and a murmur that is heard outside the cardiac region* Indeed, the findings of a pulsating mass in the lung of a person with a moderate cyanosis should always suggest the possible presence of an arteriovenous fistula In the asymptomatic cases the diagnosis is based on the roentgenologic, bronchographic, and angiographic findings Angiography is probably the most reliable method because it demonstrates the vascular nature of the disease However, it carries with it a certain amount of danger, particularly in cardiac and hypertensive patients In these patients the injected matter (Diodrast or iodopracet) may pass through the arteriovenous shunt into the *left side of the heart and the* coronary circulation without sufficient dilution in the capillaries In a few cases these injections have been fatal

Differential Diagnosis—There is some similarity between arteriovenous fistula and Rendue Osler Weber disease because both of these conditions show telangiectatic foci scattered throughout the body However the superficial similarity is overshadowed by a number of differences which are as follows

1 In Rendue-Osler Weber disease the dominant symptom is the anemia caused by recurrent hemorrhages while patients with pulmonary arteriovenous fistula do not have anemia (A pulmonary fistula has rarely been observed in Rendue-Osler Weber disease)

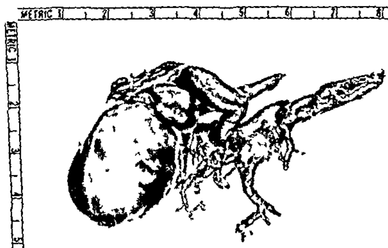


Fig 16?—The aspect of the removed left lower lobe fistula (a low melting point alloy cast)

2 The differential diagnosis between a fistula and polycythemia is evident from the absence of a splenomegaly and of hypertension in the fistula

3 The differential diagnosis between a fistula and a congenital heart disease is based on the delayed appearance of cyanosis and extracardiac murmur in patients suffering from a fistula

The possibility of a primary and a metastatic lung tumor a tuberculoma or a cystic bronchiectasis should also be considered in the differential diagnosis

Complications—The disease is occasionally complicated by a cerebral accident due to polycythemia by a rupture of the aneurysmal sac into the bronchus or pleural cavity (Bower) by a subacute bacterial endocarditis and by a pneumothorax The occurrence of a fulminating fatal hemoptysis was mentioned above

Treatment—The treatment consists in the surgical removal of the aneurysmal sac (Fig 162) but before embarking on a surgical intervention it is essential to ascertain whether there are one or several shunts present Charbon and his associates reported a case in which a second fistula was discovered in the contralateral lung 7 years after the successful removal of an arteriovenous fistula In the case of Baer and his associates 3 consecutive lobectomies were performed because of the successive discovery of 2 additional fistulas following the first operation Adams and his associates reported a case of an arteriovenous fistula which they removed by pneumonectomy on the assumption that the lesion was solitary However 9 years later another fistula was discovered in the remaining lung

III MANGIOMA

Hemangioma is a neoplasm whose parenchyma is composed of capillary spaces lined by flattened endothelial cells The tumor advances by the sprouting of the endothelial cells The spaces are circular they vary greatly in size and usually are filled with red cells clotted blood or thrombi In addition they are separated by thin strands of connective tissue infiltrated by small round cells

The neoplasm is a congenital malformation which apparently grows very slowly although in children it has been found at times to proliferate rather rapidly It is round or somewhat oval in shape doughy and surrounded by a fibrous capsule Balboa and Chesterman collected from the literature 10 benign and 25 malignant hemangiomas The consensus is however that the growth is generally benign even in those cases where an invasion of the lymph nodes or of the adjacent structures has occurred When hemangiomas are discovered simultaneously in several organs or structures of the body they are regarded as independent primary growths and not as metastases from one primary tumor Hemangiomas are often multiple

They are characteristically located in the anterior mediastinal space *i e* in the region where thymomas and teratomas are located (In fact some observers include hemangiomas in the teratoma family) Balboa and Chesterman collected from the literature 7 cases in which the tumors were mostly located in the posterior mediastinum and Grimes and his associates observed a case of a hemangioma confined totally to the posterior mediastinal space

The vascular tumor has been found in persons of all ages Of 17 cases culled from the literature 14 were found (by Seybold and his associates) in individuals less than 14 years of age One fourth of the cases occurred in children under 1 year Both sexes were affected with equal frequency

Usually hemangiomas are overlooked clinically they are disclosed by

accident during a routine roentgenological examination of the chest The x rays reveal a well circumscribed round density located in the anterior mediastinum suggesting a cyst or a neoplasm In a few cases it has been

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The circular shape of the hemangioma and the shadow it casts pose the same diagnostic problem of the "coin lesion" discussed in Chapter 2 As in the case of the coin lesions the tumor can rarely be diagnosed by clinical means alone A thoracotomy is usually resorted to and the tumor is extirpated whenever possible In cases where no invasion is present the prognosis is favorable but the prognosis is guarded when the histological picture suggests a malignant growth It has been stated by some observers that in the hemangioma the histological appearance of malignancy does not as a rule connote clinical malignancy

Sclerosing Hemangioma—These tumors are usually found in the skin and on rare occasions are observed in the parenchyma of the lung Liebow and Hubbell have recently reported 7 cases They have de

crosis and fibrosis The proliferated blood vessels form papillary infoldings into the air spaces obliterating them The lesion is also characterized by an abundance of fat cells which are typical of xanthomas with which they have been identified by some writers The few cases described in the literature have failed to elucidate the origin or the nature of the growth In fact it is even possible that the lesion is not a neoplasm but a granuloma Like the hemangioma the sclerosing hemangioma is portrayed on the x ray film as a coin lesion and as a hemangioma it poses the same diagnostic problem Clinically it is inapparent It has been observed that extirpation has been followed by permanent cure

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tumor is devoid of spaces forming solid cellular masses of spindle shaped cells characteristic of a sarcomatous growth The vascular channels are filled with blood clots or thrombi The tumor (similar to the hemangioma) advances by a sprouting of the endothelial cells which forms new capillary spaces

The new growth is round spongy and tends to invade adjacent structures It rarely has been observed in the chest but it has been found on

many occasions in other organs In the liver its origin has been traced to the Kupffer cells lining the hepatic sinusoids

Hemangiopericytoma.—These tumors are said to originate from cells lying on the adventitial coat of the blood vessels i e from pericytes (in the past the endothelial cells have been referred to as endocytes) The cells were described by the pathologist Eberth (1870) who named them "perithelial" The tumors which they allegedly produced were termed peritheliomas" Subsequent observations disproved the existence of peritheliomas but the perithelial cells or pericytes have been repeatedly described and their role has been variously interpreted (i e as muscle cells playing a role in the contraction of blood vessels or as resting phagocytic cells) *

The name "pericytes was given by the Swiss histologist Zimmermann Stout found that these cells produce neoplasms made up of capillary blood vessels surrounded by one or more layers of pericytes He termed the tumor hemangiopericytoma The tumor resembles the so called glomus tumors Hemangiopericytomas have been found in various organs including the mediastinum Benign as well as malignant varieties have been reported (The ratio between the benign and the malignant tumor is about 3 to 1) They are clinically inapparent and their discovery is usually incidental to a routine roentgenological examination of the chest They are treated by extirpation followed by radiation

PARATHYROID ADENOMA

The term "parathyroid implies closeness (para meaning near) of the parathyroid glands to the thyroid gland However parathyroid tissue is found in places remote from the thyroid namely in the mediastinum where as in the neck it is apt to undergo a neoplastic transformation and to induce symptoms characteristic of a parathyroid adenoma Cope found that of 49 parathyroid adenomas treated at the Massachusetts General Hospital 9 cases or 18 per cent were confined to the mediastinum Of this number 5 were in the anterior mediastinum and 4 in the posterior mediastinum

Most of the adenomas were situated high in the superior mediastinum They were overlooked by the roentgen rays because of their small size and their position behind the sternum or clavicle In the case of Staub and his associates the tumor was revealed by the roentgen rays as a smooth oval mass about 7.5 cm in diameter situated in front and to the left of the pulmonary artery For several years preceding admission the patient had complained of weakness lassitude and easy fatigability and for 3 months prior to hospitalization

*Fried B M The infection of rabbits with the tubercle bacillus by way of the trachea Arch Path 12 689 1931

he had had a cough associated with retrosternal discomfort The calcium level in the blood was 12 7 mg and the phosphorus level was 5 0 mg per 100 cc of blood The alkaline phosphatase activity was 6 Bodansky units

The autopsy revealed a tumor 7 cm in diameter situated in the left mediastinum beneath the second rib On histological examination the tumor was found to be a parathyroid adenoma composed of the chief cells

In the differential diagnosis of mediastinal tumors the possibility of an aberrant parathyroid adenoma should always be considered

PHEOCHROMOCYTOMA CHEMODECTOMA

The great variety of neoplasms encountered in the thoracic cavity is best illustrated by the finding there of pheochromocytomas and chemodectomas The two tumors are best examined separately

Pheochromocytoma —Neoplasms made up of cells of the so called chromaffin system usually arise (1) in the medulla of the adrenal gland *(2) in the sympathetic plexuses and (3) in association with sympathetic* ganglia These cells are derived from the neuroectoderm and are descendants of the sympathogonia

In 1865 Henle was the first to notice the characteristic tendency of these cells to take on a dark brown color when subjected to chromaffin salts (Pheochromocytoma means tumor of dark colored cells) The concept that the affinity is *sui generis* has not been borne out by further studies Observation has revealed that the process is one of oxidation namely a nonspecific reaction between epinephrine (the vasopressor substance secreted by these cells) and the strong oxidizing reagents such as a solution of potassium iodate

The term "paraganglioma is derived from the topography of the paraganglia in which the tumors originate Cells of the chromaffin system withdrawing from the neural crest accumulate on the dorsal aspect of

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testes The chief interest of these cells lies in their ability to perpetuate the vasopressor substance characteristic of the parent cell They induce intermittent or sustained hypertension

The first case of an intrathoracic pheochromocytoma was reported by *Miller in 1924 The second case was reported by Philips in 1940 and* the third by Maier in 1949 The case reported by Philips from the Pathology Department of the Montefiore Hospital was observed by me in the medical clinic of the same hospital a few years previously It concerned a man 39 years old who suffered from glomerulonephritis

and hypertension. The left supraclavicular fossa was full and tender to palpation. There was a Horner's syndrome on the left side and anhydrosis of the same side. Roentgenological examination revealed a *dense* shadow in the left apex. The picture was similar to the picture cast by a superior pulmonary sulcus tumor. However, because of the protracted course of the illness, the virtually stable character of *the process* and the lack of *clinical symptoms compatible* with cancer, the apical shadow remained enigmatic. The patient died of congestive heart failure.

The autopsy *revealed a firm round mass about 6 cm in diameter in* the apical part of the left pleural cavity. Because of the limitation of the autopsy to an abdominal incision the exact topography of the tumor could not be established with certainty. It seemed to lie astride the apex of the lung which it pushed downward. Histologically it was made up of nests of large polyhedral cells in an abundantly vascularized fibrous stroma. The diagnosis was pheochromocytoma (Fig. 163A).

Summary.—Like the sympathetic system, the chromaffin system originates from the cells of the ganglionic crest. These cells migrate toward the medulla of the adrenal and along the entire length of the autonomic nervous system, where they settle in nests in the autonomic ganglia. Here they are known as paraganglia or chromaffin bodies. In all probability the tumor in this case arose from the paraganglion that was *associated with the first left thoracic ganglion. It compressed the lung* pushing it downward and also caused pressure on the brachial plexus inducing an ipsilateral anhydrosis and Horner's syndrome. The tumor was hormonally active inducing a sustained hypertension.

Chemodectoma — Nonchromaffin Paraganglioma. — *Definition.* — The carotid body is a structure located behind the common carotid artery. It is made up of a cluster of epithelial-like cells arranged in lobules or compact masses and surrounded by a richly vascularized stroma. This structure is believed to have the function of a chemoreceptor being sensitive to changes in the pH or CO concentration of the blood circulating through its rich vascular network. *Under certain conditions it plays a* role in the regulation of respiration.

Structures that closely resemble the carotid body are present in other *locations both alongside the carotids and in the mediastinal space.* In the latter they are situated (1) near the innominate artery, (2) near the origin of the left subclavian artery, (3) on the right side of the pulmonary artery, (4) near the pulmonary end of the ductus arteriosus and (5) on the right side and posterior surface of the pulmonary trunk. Because of their structual and functional identity they are referred to as a "system of chemoreceptors" composed of nests of epithelial-like cells. The rich vascular stroma surrounding these cells *histologically* resembles the carotid body. They have been defined as nonchromaffin

paraganglions because of their location near nerve ganglions (hence, the prefix para) also, because of their dissimilarity to the chromaffin para ganglions which secrete a vasopressor substance They are not glands of internal secretion

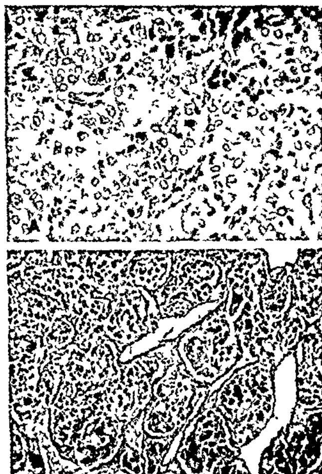


Fig 163—A pheochromocytoma of the first (left) thoracic ganglion B chemodectoma (nonchromaffin paraganglioma) of the mediastinum Clusters of cells are separated by a richly vascularized stroma

Tumors —That the carotid body may undergo a neoplastic transformation has been known since the beginning of the century but tumors of other bodies belonging to the system of chemoreceptors became known only recently It was suggested by Lattes that neoplasms arising from

the cells of this system be termed "nonchromaffin paragangliomas." Mulligan called them "chemodectomas." Seven cases of mediastinal chemodectomas have hitherto been reported: 4 by Lattes, 1 by Manto and 2 by Duncan and McDonald.

In one of Lattes's cases (his Case No. 3) the intrathoracic tumor extended from the anterior mediastinum upward behind the right clavicle and into the supraclavicular fossa. Histologically it resembled the tumors of the carotid body (Fig. 163B) and clinically it was asymptomatic until a short time before hospitalization when hoarseness, slight dysphagia and dyspnea appeared. A roentgenological examination disclosed a mediastinal mass that displaced the trachea and esophagus. In another of Lattes's cases (his Case No. 4) the tumor was found in a 35 year old male who had died of bulbar poliomyelitis. The tumor, about 1.5 cm. in diameter, was loosely attached to the arch of the aorta near the site of the obliterated ductus arteriosus. It is noteworthy that the patient had two more independent tumors of the carotid body type, one located on the vagus nerve in the region of the ganglion nodosum and the other at the bifurcation of the carotid artery. The mediastinal tumor was clinically nonapparent.

In Duncan and McDonald's first case the tumor was discovered at an army induction center. It concerned a man 18 years old who complained of pain across the abdomen, particularly in the upper right quadrant. A roentgenological examination showed a rounded mass measuring 6.4 cm. in diameter in the right posterior portion of the thorax adjacent to the spinal column at the level of the ninth and tenth vertebrae. The tenth rib was eroded. The tumor removed surgically measured 7 × 4 × 4 cm. and weighed 50 gm. It was round, smoothly lobulated and covered with large dilated vessels. The authors noted that the new growth was related to the descending thoracic aorta on the right. Chemoreceptor tissue in this area had not been previously reported.

Duncan and McDonald's second case referred to a woman 33 years old in whom a routine roentgenological examination disclosed a smooth rounded mass in the right posterior mediastinum adjacent to the spinal column at the level of the sixth, seventh and eighth ribs. Histologically the removed tumor was identical with that described in the first case. It was composed of small and large nests of cells that were separated by connective tissue septa containing numerous thin walled vessels. There were no mitoses. After remaining well for a period of 14 years the patient developed symptoms suggestive of a transverse lesion of the spinal cord. Roentgenological examination revealed a large ovoid paravertebral mass in the seventh thoracic vertebra as well as a total destruction of the vertebra. It was not ascertained whether the newly discovered mass was related to the growth that had been removed 14 years before.

Tumors of this kind have rarely been observed in the thoracic cavity, but as in other instances, a greater awareness of their existence will eventually lead to a more frequent identification of these neoplasms

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Chapter 15

Tumors of the Pleura

Mesothelioma

The Pleura.—The pleural cavities are closed spaces walled off by the pleural leaflets *viz* (1) the parietal or costal which enclose the ribs and their cartilages (2) the visceral which cover the surface of the lungs (3) the mediastinal which are applied to the mediastinum (4) the diaphragmatic which cover the diaphragm and (5) the cervical which rise to the neck The mediastinal pleura unites with the visceral pleura at the hilus of the lungs to form the pulmonary ligament which envelops the pulmonary vein the pulmonary artery and the pulmonary lymphatics

The pleural leaflets are covered by a layer of squamous cells (the mesothelium) beneath which lie collagenous fibers arranged in fascicles and parallel rows and smooth muscle fibers which run in parallel and perpendicular bundles also elastic fibers blood vessels and lymph vessels The mesothelium is a layer of squamous cells that covers the surface of all serous membranes *e g* the peritoneal the pericardial and the pleural. This layer is made up of typical epithelial cells which arise from the mesoderm (The lining of the pleuroperitoneal cavity develops from coelomic epithelium which is split off from the mesoderm)

The pleural cavity drains into the mediastinum Like the omentum the pleura abounds in phagocytic macrophages gathered in foci (similar to the so called *tâches laiteuses* or milky spots found in the omentum by Ranvier) These scavenger cells are scattered beneath the stratified mesothelial layer where they display their customary phagocytic functions For instance India ink introduced into the pleural cavity appears beneath the mesothelium within a few hours after injection and is instantaneously attacked by the macrophages which proliferate and flock to the foreign matter and phagocytose it Suspensions of bacteria introduced into the pleural cavity undergo the same fate It is believed the pleural draft tends to convey the bacteria into the subpleural phagocytic foci (Kampmeier pointed out their presence there) where they are taken up by the macrophages and destroyed The phagocytic cells seem to predominate in the mediastinal pleura

The arteries of the pleura are derived from the intercostal, internal mammary, musculophrenic, thymic, pericardial, pulmonary, and bronchial vessels

The parietal pleura receives its innervation from the intercostal and sympathetic nerves, and the visceral pleura receives its innervation from the pulmonary plexuses which originate in the vagus and the sympathetic nerves The diaphragmatic pleura is penetrated on the outer side by the lower six intercostal nerves and centrally by the phrenic nerve fibers

TUMORS

In the past a variety of unusual tumors have been traced to the pleural leaflets Recent investigations have reduced the "variety to two main types (1) diffuse mesothelioma, characterized mainly by the tendency of the neoplastic mesothelial cells to spread over the entire surface of the leaflet, covering it in a blanket-like manner, (2) localized mesothelioma, i e, a solitary tumor which is localized and well circumscribed The localized tumors have been described under various names, such as sarcomas, fibrosarcomas, leiomyosarcomas, giant sarcomas, and fibromas At present they are reported under the names of "Localized Pleural Mesothelioma," and 'Solitary Pleural Mesothelioma" The two types are best examined separately

Diffuse Mesothelioma—Adami was probably the first to call these tumors "mesotheliomata' and among the first to point out their origin from the mesothelial cells McCallum stated that "these tumors are apparently primary in the lining cells of the pleura" According to Borst, tumors of the pleura "concern a peculiarly propagating tumor which grows diffusely over serous surfaces and is accompanied by intense inflammatory manifestations, i e, exudate formation and adhesions The entire membrane is covered with flat or prominent nodules, also with polyps and papillae which are made up of neoplastic tissue The pleural surface becomes diffusely thickened and hardened The new growth remains on the surface without invading the lung"

The literature of the past 50 years abounds in reports of cases of mesotheliomas (also called pleural endotheliomas) Robertson, in a scholarly analysis of these cases reached the conclusion that with very few exceptions they were not primary mesothelial tumors, but rather neoplasms that had metastasized to the pleura, chiefly from the lungs The opinion of Robertson was not universally shared, but it was agreed that primary mesothelioma is a very rare tumor indeed In 3,533 autopsies performed at Temple University, Campbell and Penner, for example, discovered only 4 cases It was moreover accepted that whenever the pleura is invaded diffusely by a tumor, the possibility of the neoplasm being a metastasis should be considered first

Early Phases—The incipient phases of the growth have not been hith erto observed or recorded A mesothelioma (like other tumors) probably starts at one point of the pleura from where it propagates The manner of its diffuse spread is due to the topography tumors that have arisen in a serous membrane (as well as those that have metasta sized to such a membrane) tend to spread over the surface *i e* along lines of least resistance Then too the manner of spread may be due to the biological properties of mesothelial cells to cover surfaces Malig nant cells imitate their normal somatic progenitors in many ways

Benign and Malignant—As already stated the neoplasm covers the entire surface of the leaflet in a blanket like manner leading to its manifold thickening and hardening The affected pleura is firmly adherent to the lung Although in many cases the growth remains confined to the pleura in many others it invades the surface of the lung and sometimes sends out prong like extensions to the center of the lung Indeed the relatively benign types remain *in situ* while the malignant types are invasive locally and distally sending out metastases to remote organs Metastases are found in the lymph nodes pericardium thoracic wall diaphragm and peritoneum The spread is probably by way of the serosa (serosal seeding) and along the lymph channels Dawe de scribed a case with widespread hematogenous metastases I observed a case of a diffuse mesothelioma which involved the serosa of the small bowel from where it penetrated the muscularis mucosa causing an obstruction of the intestinal lumen A small metastatic nodule obviously of hematogenous origin was found in one vertebra

Histology—The histology of the tumor is of particular interest It is made up of two components epithelial and fibroblastic the latter imi tating a sarcoma It is possible that this feature induced some former pathologists to designate it as carcinosarcoma The mucus secreting epithelial cells (? hyaluronic acid) from tubules or acini which are

arose from the mesothelial cells which are of mesodermal origin Maximow s investigations are cited in support of this concept Maximow noticed that in tissue cultures a portion of the implanted serosal cells evolves into true epithelial cells while in other portions of the culture

diffuse

w data

are available concerning early manifestations Formerly cases would come to autopsy undiagnosed In the later stages where diagnosis is merely of academic interest patients show considerable loss of weight and complain of pain in the chest and of dyspnea X ray films show an

almost diffuse shadow of the entire hemithorax The findings of physical examination are characteristic of an obliterative pleuritis, the hemithorax is shrunken and narrowed, with narrowing or complete obliteration of the intercostal spaces On auscultation there is absence of breath sounds and of tactile fremitus It has been stated that at a thoracentesis the needle in these cases meets a characteristic resistance not observed in other conditions This, however, cannot be relied upon A fibrothorax of long standing caused by a pathogen or by the tubercle bacillus also yields a firm and thick pleura which is as difficult to puncture as is the pleura thickened by the mesothelioma

In instances in which the pleural cavity is not totally obliterated, a hemorrhagic fluid accumulates in the pocket This fluid should be investigated for neoplastic cells in paraffin sections as well as by the method of Papanicolaou

The early signs of the disease can only be conjectured There is probably little doubt that the tumor implanted on the pleura (even when still strictly localized) will induce disturbances in the pleural cavity and probably also in the respiration Awareness and diligent clinical and roentgenological studies are the prerequisite in the diagnosis of the incipient stages

Mesotheliomas are treated surgically Nitrogen mustard has been observed to afford good palliation in some cases

Localized (Fibrous) Mesothelioma—Unlike the diffuse pleural mesotheliomas, which are characterized by a growth scattered over the entire serosal surface, the localized pleural neoplasms appear as solitary and circumscribed tumors surrounded by a fibrous tissue capsule attached to the lungs by a pedicle or to the chest wall by vascular adhesions (Fig 164) They take origin in the parietal or in the visceral pleura Of 24 cases described by Clagett and his associates 18 arose from the visceral pleura and 6 from the parietal pleura They may be benign or malignant, the former project into the pleural cavity and the latter are locally invasive and usually do not project therein In the past when x-ray examinations were not used or were used sparingly, undisclosed voluminous tumors were encountered Large ones are still occasionally found, as demonstrated by the case of Hawthron and Frobese, who recently removed a tumor weighing 1,500 gm

Histologically the benign growth is made up of spindle (fibroblast-like) cells which are uniform and show no mitoses The stroma abounds in reticulin and in collagen (Figs 165 and 166) Often the structure resembles a myoma or a leiomyoma The malignant types are also composed of spindle cells, which are not of uniform size, but show mitoses, and a stroma poor in reticulin and in collagen The localized tumors (i e, the benign as well as the malignant) contain no *epithelial cells*



Fig 164 —*A* fibroma of pleura *B*, histology of the tumor

Fig 165 —Localized pleural mesothelioma posteroanterior and right lateral views



Fig 166 —Structure of the tumor

The histogenesis of the localized mesothelioma is debatable It has been generally accepted that unlike the diffuse mesothelioma which originates from the serosal mesothelial cells localized pleural neoplasms arise from the subserosal connective tissue Stout however has stated that both diffuse *and* localized tumors originate from one source viz from the serosal mesothelium His opinion is based on the following Murray (in his laboratory) observed that when the fibroblastic cells from a localized fibrous pleural tumor had been grown on an artificial

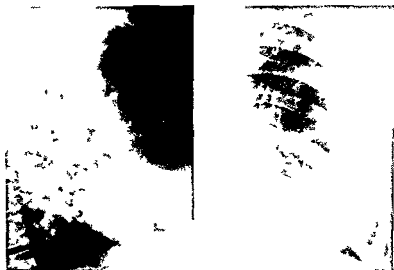


Fig 167 —Localized pleural mesothelioma in the basal portion of the right lung posteroanterior and lateral views

medium they assumed the aspect of mesothelial cells Stout combined this observation with the findings of Maximow cited above (that in tissue cultures mesothelial cells often assume features of fibroblasts) and concluded that the whole group of pleural tumors should be regarded as mesothelial derivatives examples of the versatility of the mesothelial cells Both the benign and the malignant mesotheliomas may grow diffusely (*i e* as diffuse mesotheliomas) or form solitary masses (*i e* as localized fibrous mesotheliomas)

The case to follow is of interest in this respect It concerned a man 63 years of age who was referred to the chest clinic of the Morrisania City Hospital for a checkup He had had a nonproductive nocturnal cough for 5 years and had been moderately dyspneic for the immediately preceding year

On physical examination he appeared to be obese, and his chest was barrel shaped. The lungs were hyperresonant and scattered rales were audible in different areas of both lungs. There was no history of hemoptysis, of chest pain, or of loss of weight.



FIG 168.—Localized pleural mesothelioma in the interlobar fissure between the middle and lower lobes of the right lung.

On x-ray examination of the chest a well circumscribed oval density was found in the basal region of the right lung (Fig 167) "midway between the mesial and lateral borders and also midway between the anterior and posterior borders. The diagnosis of a neoplasm was made and the patient was referred to the hospital for treatment.

On thoracotomy a cystic tumor measuring $3.0 \times 3.0 \times 3.5$ cm was found in the interlobar fissure between the middle and the lower lobes of the right lung (Fig 168). It was attached to the visceral pleura by a broad pedicle, was firm, lobulated, and encapsulated.

Histologicalh the tumor was made up of a very loose textured stroma orming acinar like structures lined by swollen and hyperplastic meso helial cells also by cystic structures lined by similar cells (Fig 169) The mesothelial structures secreted a mucoid matter (? hyaluronic acid) The histology of the tumor is of interest because similar (i e localized umors) have in the past been described as characteristically made up of

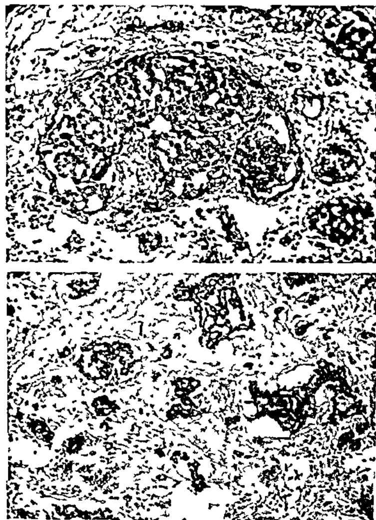


Fig 169 —Swollen mesothel al cells forming acinar structures also cystic structure lined by s milar (mesothelial) cells The stroma is loose textured

fibroblasts only, and only diffuse mesotheliomas are composed of two types of cells

Here then is a localized tumor which would be acknowledged to have arisen in the subserosal connective tissue, and yet contained mesothelial cells

The case probably corroborates the unitary histogenetic concept of pleural mesotheliomas as expressed by Stout and his associates

The tumor was benign The patient is well 6 years after the pneumonectomy

Clinical Manifestations—Solitary mesotheliomas are very slow-growing tumors The fact that tumors of from 2 to 5 kg in weight are observed attest to their leisurly growth and to the barely noticeable symptoms which they produce Large tumors compress the lung gradually and the symptoms which they produce are usually due to pressure and distortion of the bronchus, causing bronchostenosis and atelectatic pneumonitis They have been known to compress the superior vena cava, inducing the superior vena cava syndrome, or to impinge on the recurrent laryngeal nerve causing hoarseness Sirot reported a case in which symptoms of *cor pulmonale* ensued as a result of pressure of the tumor on the heart Pleural effusion is a frequent accompaniment of these tumors

When the solitary tumor is still small, the symptoms it causes are usually disregarded by the patient These consist of a mild cough, occasional moderate elevation of temperature, and mild chest pain

Of interest is the occurrence of clubbing of the fingers and of osteoarthropathy Patients complain of intense pain in the joints which often are swollen and tender The "rheumatic" pains usually precede the appearance of the pulmonary symptoms The articular symptoms, the clubbing of the fingers, and the osteoarthropathy disappear following the removal of the tumor

Physical examination is certainly not sufficient alone to establish the diagnosis Even with roentgenological examination the diagnosis cannot be made with certainty Hamartomas, adenomas, primary or metastatic tumors, and pericardial cysts yield quasi similar pictures Thoracotomy is the sole means of ascertaining the diagnosis The tumor is eradicated surgically

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TUMORS of the MEDIASTINUM

Chapter 16

Mediastinal Tumors

The Mediastinum.—The mediastinum is a space or cavity between the right and left pleural cavities which contains all the thoracic viscera except the lungs It is lined on both sides with the (mediastinal) pleura and is divided into four compartments (1) superior, (2) anterior, (3) middle, and (4) posterior (Fig 170)

The superior mediastinum is the region above the plane that joins the sternal angle to the intervertebral discs, between the fourth and fifth

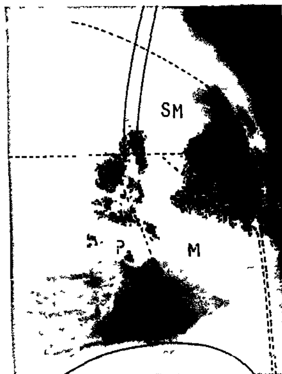


FIG 170—Diagramatic division of the mediastinal space into four compartments Bronchiogenic cancer present in superior mediastinum (SM)

thoracic vertebrae It contains the trachea, the esophagus, the thoracic duct, the thymus gland, the arch of the aorta, the innominate artery, the thoracic portion of the left common carotid, the left subclavian arteries the innominate vein, the upper half of the superior vena cava, the phrenic nerve, the vagi, and the left recurrent laryngeal nerve

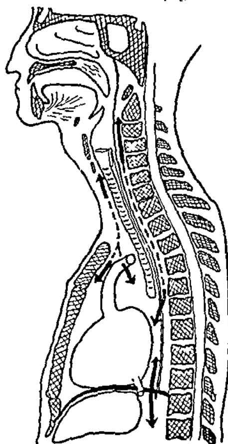


FIG 171 —Shows direct communication of the mediastinal space with tissues of the neck and retroperitoneum (Kornblum, K, and Osmond, L H Mediastinitis, *Courtesy of Amer Jour Roentgenol 32, 23 1934*)

The anterior mediastinum is the space between the sternum and the pericardium which is walled off on each side by the pleurae It contains adipose and areolar tissues, as well as lymphatics, lymph nodes and the thymus gland

The middle mediastinum contains the heart and the pericardium, the ascending aorta, the lower segment of the superior vena cava, the bifurcation of the aorta, the trachea, the two main bronchi and bronchial lymph nodes, the bronchial artery with its branches, and the phrenic nerve

The posterior mediastinum is the space between the middle mediastinum and the vertebral column It is bounded by the heart above, by the

pericardium in front by the posterior surface of the diaphragm below and is walled off by the mediastinal pleura on either side It contains the thoracic part of the descending aorta the azygos and hemiazygos veins the esophagus and the sympathetic and splanchnic nerves

The mediastinal space is the seat of the lymph nodes It is also the opening for the passage of the esophagus the aorta the thoracic duct the azygos veins and the splanchnic nerves The esophagus passes behind the trachea anteriorly to the right of the descending aorta The superior vena cava with its tributary the azygos vein is situated on the right The azygos vein enters the superior vena cava above the right main bronchus

Mediastinitis —The mediastinal space communicates with the structures at the base of the neck and with the retroperitoneal space When these areas are affected by a pathogenic disease the pathogens may reach the mediastinal space and induce a mediastinitis *i e* an inflammation of the mediastinal areolar tissue This process may also result from affected mediastinal lymph nodes In fact there is a direct relationship between certain tracheobronchial lymph nodes and the localization of the disease in the mediastinum The lungs too are in communication with the mediastinal space by way of the pulmonary broad ligament (Fig 171)

Formerly clinicians stressed the possibility that syphilis and tuberculosis may be the main if not the sole cause of mediastinitis but recent observers have disclosed multiple etiological factors namely trauma infection and neoplasms

TUMORS

The mediastinal space is the seat of primary and metastatic tumors and also of cysts which are chiefly congenital (Table 19) Neoplasms and cysts are found in the mediastinum much more frequently than has been

Table 19 Primary Tumors and Cysts in the Mediastinal Space

Tumors		
Benign	*Malignant*	*Cysts*
Thymogenic	Lymphoid tissue	Dermoid
Thymoma	Reticulum-cell sarcoma	Bronchogenic
Neurogenic	Lymphosarcoma	Pericardial coelomic
Neurinoma	Hodgkin's disease	Gastroenteric
Neurofibroma	Thymogenic	Esophageal
Ganglioneuroma	Thymoma	Thymic
Neuroblastoma	Neurogenic	Lymphangioma
Vascular	Neurinoma	Meningocele
Hemangioma	Neurofibroma	
Endocrine	Neuroblastoma	
Parathyroid adenoma	Ganglioneuroma	
Thyroid adenoma		
Goiter		

recorded They can be readily located and are frequently treated with success

The mediastinum is a frequent seat of metastatic tumors Pulmonary abdominal and mammary cancers invade the lymph nodes often producing pictures characteristic of primary mediastinal neoplasms (Fig 172)

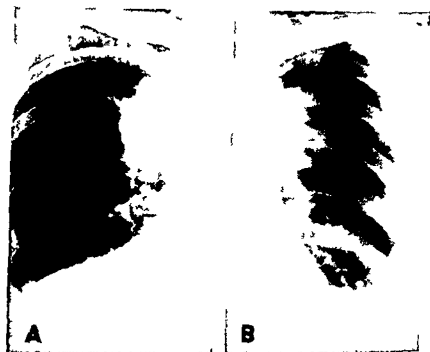


Fig 172—A thymoma B unilateral metastasis of mammary carcinoma to hilu lymph nodes

TUMORS OF LYMPHOID TISSUE

Lymphomas are probably the most common type of tumors encountered in the mediastinal space This is because of the abundance of lymphoid tissue present in this region particularly in the middle mediastinum These neoplasms are made up of cells derived from the middle embryonic layer i e the mesenchyma

Neoplasms arise from primitive reticulum cells (reticulum cell sarcomas) as well as from their descendants the lymphoblasts (lymphoblastomas) lymphocytes (lymphosarcomas) and plasma cells (plasmacytomas)

RETICULUM CELL SARCOMA

Pathological Aspects—For a long time pathologists have been familiar with the large round cell sarcoma the origin of which they could not

satisfactorily trace In 1913 Ewing suggested that its source was probably the reticulum cell It was not until the individual publications of first Roulet and then Oberling that the tumor was recognized as a separate entity and named "reticulum cell sarcoma

Although the reticulum cells are scattered throughout the body, they are found in the lymph nodes in wide agglomerations They make up the bulk of the stroma as well as the germinal centers of the nodes In most instances therefore the sarcoma arises in the lymph nodes In 24 of 48 cases studied by Jackson and Parker the sarcoma arose in the lymph nodes 9 in the retroperitoneal 6 in the gastrointestinal 1 in the iliac 2 in the cervical and 3 in the mediastinal nodes Only 1 originated in the bones 1 in the tonsils and 1 in the spleen

The relationship between reticulum cell sarcoma and lymphosarcoma has been a subject for discussion One group of investigators maintained that the reticulum cell sarcoma is an autonomous clinical and pathological entity another group stated that it is a form of lymphosarcoma and therefore applied the term "lymphosarcoma of the reticulum cell type" or "reticulum cell lymphosarcoma"

Although the genetic relationship between the two types of sarcoma is not contested, clinically they present distinct entities Reticulum cell sarcoma may arise in the skeleton and in the central nervous system * while lymphosarcoma has not been known to originate in either of these sites

The age incidence is likewise at variance A generalized reticulum cell sarcoma of the lymph nodes appears most frequently in persons between the ages of 50 and 70 Only the sarcomas that originate in the skeleton are encountered in those under 20 years of age Lymphosarcoma has two peaks The incidence in the first peak is up to the age of 10 and in the second between the ages of 50 and 60

Unlike lymphosarcoma which is often accompanied or followed by lymphatic leukemia reticulum cell sarcoma has not been observed to show leukemic changes in the blood

The cells in reticulum cell sarcoma resemble the parent cells morphologically displaying ameboid phagocytic properties (Fig 175)

Clinical Aspects —Reticulum cell sarcoma is a malignant metastasizing tumor (Figs 174 and 175) In a series of cases studied by Jackson and Parker the tumor invaded the liver in 10 cases the pancreas in 9 the spleen in 8 the adrenal glands in 7 the heart in 5 and the lungs in 6 The pulmonary metastases consisted of numerous scattered nodules Pleurisy with effusion was found in about 7 per cent of the cases

The initial manifestations of the disease are revealed in the appearance

*The first case of reticulum-cell sarcoma of the brain was reported in 1926 See Fried B M Sarcomatosis of the brain Arch Neurol & Psychiat 15 205 1926



Fig 173 —Reticulum cells of the bone marrow



Fig 174 —Reticulum cell sarcoma of the mediastinum Cut surface

of cervical lymph nodes The nodes usually are firm attached to the overlying skin and resemble metastatic carcinomatous nodes

The symptoms are protean and at the onset are not pathognomonic Weakness anorexia and various other characteristics of malignant diseases occur In the more advanced stages pain in the chest dyspnea

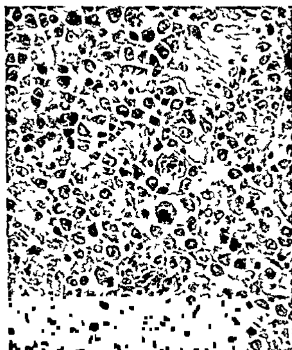


Fig 175—The histology of the reticulum cell tumor illustrated in Fig 174

hoarseness and epistaxis are present On percussion one notices a widening of the area of flatness of the mediastinal space The diagnosis is essentially based on a biopsy of an accessible lymph node

LYMPHOSARCOMA

Lymphosarcomas originate from lymphocytes or lymphoblasts As a rule they start in one lymph node or they may appear in many lymph nodes simultaneously The cervical abdominal and mediastinal lymph nodes are considered to be the most common initial sites (Fig 176)

When a lymphosarcoma originates from a mature lymphocyte it forms a new growth which is defined as "lymphocytoma" (lymphosarcoma

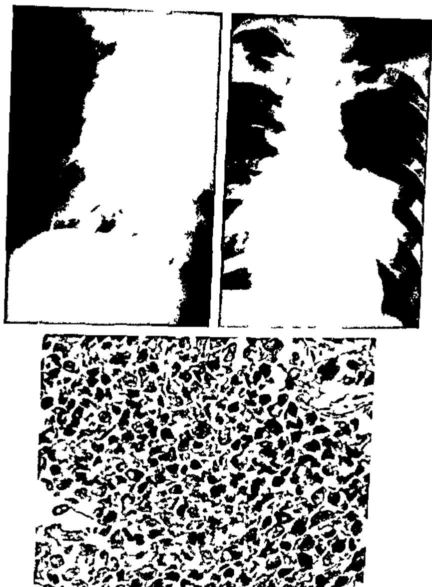


Fig 176—Mediastinal lymphosarcoma

lymphocytic type) The lymphocytoma usually destroys the normal structure of the node and infiltrates the capsule but does not metastasize to distant organs

The immature lymphoblast produces a "lymphoblastoma" (lymphosarcoma lymphoblastic type) which is locally invasive and metastasizes to distant lymphoid and nonlymphoid organs *i e* the heart lungs liver

kidneys bone marrow and skin Both the lymphocytomas and the lymphoblastomas are accompanied by a leukemic blood picture in about 30 per cent of cases

Some observers consider the distinction between the two types to be arbitrary because it depends upon the degree of differentiation of the malignant cells alone However it is of significance in the evaluation of the immediate prognosis

Lymphosarcoma occurs with greater frequency in persons of middle and past middle age In 51 per cent of the lymphocytoma cases and 65 per cent of the lymphoblastoma cases observed by Gall and Mallory the disease occurred in persons over 50 years of age

The incidence in the male sex outnumbers the female 2 to 1

From Table 20 it can be seen that out of 73 adults with lymphosarcoma the mediastinal lymph nodes were involved 15 times or 20 5 per cent

Table 20 Organs Involved by Lymphosarcoma

Organs	*No of Cases*
Lymph nodes	[illegible]
Tonsils	17
Mediastinum	15
Gastrointestinal tract	4
Bones	3
Lungs	2

Clinical and Pathological Aspects —When found in an accessible site such as the neck the nodes are almond shaped moderately soft (because of the high cellularity and scant stroma) painless and arranged in chains In the thoracic cavity where they are located predominantly in the upper mediastinum and at the root of the lungs they are arranged in clusters that are matted together (Fig 177)

The malady first passes through a "silent" or inapparent phase the duration of which cannot be determined It usually is revealed when a node appears on the surface or when mediastinal structures are being compressed The higher up in the mediastinum the nodes are located the sooner they will begin to manifest themselves because of the anteroposterior narrowness of the superior mediastinal space Similarly anterior mediastinal tumors manifest themselves earlier than middle or posterior mediastinal tumors With the increase in size the neoplastic nodes have a tendency to spread over the pericardium and the heart to compress one or both lungs and even to invade the lungs and the pleura Of 239 cases of lymphosarcoma Vieta and Craver found involvement of the lungs in 24 per cent and involvement of the pleura in

about 10 per cent The parietal pleura was found to be invaded in 30 per cent of the cases

Pulmonary lesions consist of isolated nodules or diffuse infiltrations Involvement of the pleura by large masses of tumor is quite characteristic Pleural effusions, due to involvement of the pleura or to pressure on intrathoracic veins by enlarged nodes, are not rare However, involvement of these structures is a manifestation of the advanced stages of the disease In its earlier stages, the symptoms are chiefly

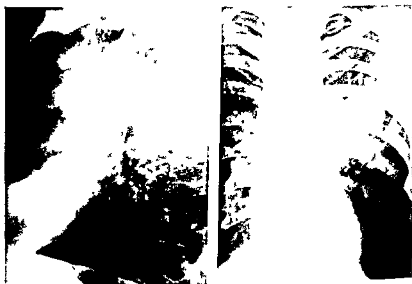


FIG 177 —Mediastinal lymphosarcoma spreading from hilus to lung posteroanterior and lateral views

systemic and essentially caused by the malignant nature of the disease Indeed, even in the incipient, inapparent phases, anemia weakness lassitude, and dyspnea on moderate exertion are the symptoms complained of most frequently

Examination in cases of lymphosarcoma reveals a widening of the area of dullness in the upper mediastinum, because of the enlarged nodes which grow from the midline in both directions Cough and signs of pressure on the mediastinal structures supervene with the advancement of the disease Roentgenological examination of the chest, supplemented by a biopsy of an accessible node, bone marrow, or spleen will reveal the character of the disease Indeed, both tests are essential —the x ray, in order to localize the mass, and the biopsy, in order to ascertain its structure When removal of tissue for diagnostic purposes cannot be performed, a therapeutic test by radiation is practiced Lym

phosarcomas are radiosensitive while thymomas teratomas cysts and metastatic or primary carcinomas are only slightly affected by radiation if at all

HODGKIN S DISEASE

Since Hodgkin published his paper in 1837 the disease which bears his name has been described by a variety of names among which are lymphadenoma, malignant lymphoma lymphoma lymphogranulomatosis and malignant granuloma In recent years however there has been a tendency to employ the term "Hodgkin s disease a suggestion originally made by Wilkes in 1867

Pathological Features—The etiology of the disease remains unknown and investigators are still uncertain as to whether it is of a neoplastic or an inflammatory nature that is caused by a virus

The main histological characteristic of Hodgkin s disease is the presence of Sternberg Reed giant cells in the tissues In the opinion of some observers it is a *conditio sine qua non* The lesion can be recognized in its early stages by the proliferation of reticulum cells some of which evolve into epithelioid cells and others into giant cells The mature lesion represents a "melting pot of cellular elements *viz* reticulum cells Sternberg Reed giant cells lymphocytes lymphoblasts myelocytes plasma cells and eosinophiles Occasionally one variety will predominate Another feature of the disease is the scattered areas of necrosis of the involved gland followed by fibrosis

The classification of the disease into three categories *i e* paragranuloma granuloma and sarcoma—although not universally adopted— is useful

The paragranuloma is characterized by the appearance of superficial cervical lymph nodes which are firm painless and outwardly normal but closer study will show infiltration with lymphocytes and characteristic Sternberg Reed giant cells As a rule the mediastinal lymph nodes in these cases are not involved The disease runs a protracted course and resembles an infective process rather than a neoplastic one

The most frequently encountered Hodgkin s granuloma is made up of various cells But unlike the paragranuloma it affects virtually every organ except the central nervous system *i e* the internal lymph nodes the bones and the visceral organs The lymph nodes show destruction of their structure invasion of their capsule necrosis and fibrosis Tuberculosis with a simultaneous involvement of the lymph nodes is frequently encountered Fever (Pel Epstein type) leukocytosis and pruritus often accompany the disease The symptoms are viewed as favoring the concept that the malady is pathogenic rather than neoplastic

Hodgkin s sarcoma an invasive and destructive disease of middle and past middle age is made up of large mononuclear cells reticulum

cells, lymphocytes, plasma cells, and Sternberg Reed giant cells It has a tendency to propagate widely and to affect any organ, including the central nervous system

Two varieties may coexist in one individual and even in the same gland While a less malignant type may be transformed into a more malignant type during the course of the illness, the reverse of this has not been observed

INTRATHORACIC

Mediastinal

Hodgkin s disease affects the lymphoid as well as the nonlymphoid organs Sternberg found involvement of the liver in 38 per cent of cases studied and involvement of the spleen in 80 per cent Of 63 cases of Hodgkin's granuloma, Jackson and Parker found the spleen to be affected in 47 instances, the liver in 31, and the bones in 35

The fact that the mediastinal lymph nodes are usually involved is widely known In the above mentioned 63 cases of Hodgkin's granuloma, Jackson and Parker found these nodes to be diseased in 59 instances In 9 cases, the mediastinal lymph nodes were found to be the primary sites In 32 cases of Hodgkin's sarcoma the same authors found that the mediastinal lymph nodes were involved 14 times and in 1 of these cases the disease seemingly originated in a mediastinal lymph node In many instances the process was confined to 1 group of lymph nodes only Thus in 19 of 77 cases studied by Kasbach none showed involvement of the peripheral nodes This observation is of importance because a negative finding in 1 node does not exclude the presence of the disease in other nodes

Hodgkin s disease primarily and predominantly affects the lymph nodes of the middle mediastinum which are seen as round or oval masses at the hilus of the lungs The belief that the paratracheal nodes are the site *par excellence* has not been sustained (Fig 178) The lymph nodes of the anterior mediastinum may be the first and only ones to be involved (Fig 179) Embleton and Blades described instances where homogeneous sharply demarcated masses were confined to the anterior mediastinum In Salzman s case the anterior mediastinal tumors were solitary, round, and located on the right side of the midline No disease was found in the middle mediastinal lymph nodes

Thomson in a study of a large number of cases arrived at the conclusion that Hodgkin s disease originates in the thymus gland *i e*, in the anterior mediastinum However, when Hodgkin's disease is found in the retrosternal lymphoid tissue, in all probability it has reached this area from the middle mediastinum



Fig 178—Hodgkin's disease of the mediastinum showing involvement of the paratracheal lymph nodes

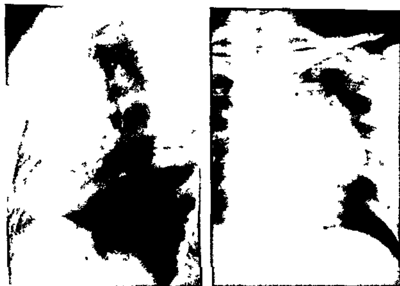


Fig 179—Hodgkin's disease of the anterior mediastinum posteroanterior and lateral views

Lungs and Bronchi

The Lungs.—The lungs are affected by Hodgkin's disease with comparative frequency (Fig 180) At the Memorial Hospital in New York, pulmonary involvement was found in 38 5 per cent of the cases At the Boston City Hospital, roentgenological evidence of lung involvement was noted in 14 per cent of cases, while at autopsy 41 per cent were identified In 3 cases of granuloma, autopsy revealed 1 case in which the lungs were involved, in 63 cases of paragranuloma there were 25



Fig 180 —Hodgkin's disease spreading from the hilus to the parenchyma of the lung

cases of lung involvement, and in 32 cases of Hodgkin's sarcoma there were 10 cases with the disease in the lungs As a rule, the lungs were invaded from the mediastinal lymph nodes

There are cases on record where Hodgkin's disease was presumed to have originated primarily in the lungs Weber, for instance, found a voluminous tumor in the lung of a woman, 73 years old Since he failed to discover abnormalities in other organs, he assumed that the disease was primarily of pulmonary origin

In a case reported by Moolten, the disease, to all appearances, had started in the lungs Jackson and Parker also outlined a case where they believed that the lung was the primary seat of the disease Kirklin and Hefke, in one of their cases, found that the lung was the only organ affected They discovered a round circumscribed area of density that was indistinguishable from a single sarcomatous or carcinomatous metastasis Yardumian and Meyers reported a case of a man, 52 years old who, on admission to the hospital, showed slight cyanosis, small,

nations were repeatedly neg tive On x ray examination extensive les ons suggestive of neoplasm or infection with *Mycobacterium tuberculosis* were found in both lungs At autopsy the lungs revealed the

s

cells The mediastinum was not affected



Fig 181 —Affection of paratracheal lymph nodes by Hodgkin s disease also spreading from mediastinal lymph nodes Unilateral spread to the periphery

Mode of Invasion —While the problem of the primary and sole involvement of the lungs by Hodgkin s disease has not as yet been convincingly established pulmonary invasion from mediastinal lymph nodes is universally conceded (Fig 181) The lungs are reached via several avenues namely (1) by contiguity (2) by way of the blood stream (hematogenous spread) (3) by way of the lymphatics (lymphatic spread) and (4) by way of all three avenues

In the pulmonary parenchyma Hodgkin s disease assumes a variety of aspects as follows

cells, leading to their manifold thickening, and the alveolar sacs, which are filled with these cells, form a granulomatous, pneumonia-like exudate

Capillaries, lymphatics, veins, and arteries (to a lesser degree) participate in the process Granulomatous elements are found in the wall of the aorta, the vena cava, and in both the jugular and innominate veins In a case studied by Simmons, the growth had replaced the greater part of the right auricle, and a finger-like mass had protruded into the cavity from the wall of the superior vena cava



Fig 185—The histology of Hodgkin's disease of the lungs

Pleura—The pleural leaflets are usually reached from the mediastinal lymph nodes, although there have been instances reported wherein a granulomatous "pleuritis" was present without the involvement of the mediastinal lymph nodes French clinicians speak of a predominantly pleural Hodgkin's disease Favre and Croizet have stated that the "infiltration may produce a granulomatous corticopleuritis" Ten of the 63 cases of Hodgkin's granuloma studied by Jackson and Parker showed involvement of the pleura

Whenever the pleura becomes affected, it is accompanied by a unilateral or bilateral pleural effusion, which closely resembles the effusion caused by carcinoma The fluid is usually clear, straw-colored, and rich in fibrin A hemorrhagic exudate has been observed in a few instances A chylothorax described by Edsa … tributed to the compression of the thoracic duct or, possibly to … tant tuberculosis

In cases where the eti… e, it should always be regarded as having p… in's disease

GIANT FOLLICLE LYMPHOBLASTOMA

Microscopically the disease is characterized by abnormally enlarged, and increased number of germinal follicles (Fig 186) A peripheral lymphadenopathy appears almost simultaneously in the axillae, the supra and infraclavicular fossae and in the groins Whether the peripheral lymphadenopathy is accompanied by similar enlargements of the lymph nodes within the body cavities has not been ascertained The

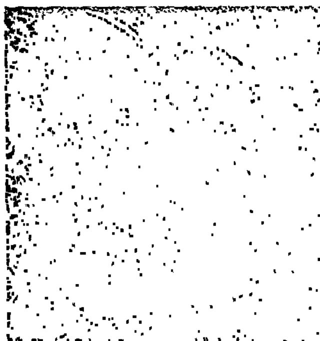


Fig 186 —Giant follicle lymphoblastoma

cells in the hyperplastic follicles are pleomorphic, and they infiltrate the capsule as well as the pericapsular fat Usually there occurs an obliteration of the normal structure of the gland, which shows an even distribution of the follicles throughout the cortex and the medulla

Giant follicle lymphoblastoma is observed in several forms i e, lymphocytic lymphoblastic, reticulum-cell and as Hodgkin's disease In most instances it eventually assumes the form of lymphatic leukemia, reticulum cell sarcoma or Hodgkin's disease, and disseminates throughout the body

Giant follicles are found in the lungs, and effusions are found in the pleural cavities in from 10 to 15 per cent of cases It is of interest that, unlike other malignant lymphomas, it tends to produce chylous pleural exudates in about 11 per cent of cases (Gall *et al*) Of 76 cases studied at the Armed Forces Institute of Pathology, Rappaport and his associates found that the lungs were involved 20 times, and the mediastinal lymph nodes were involved in 38 instances

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Chapter 17

Tumors of the Thymus Gland

THE THYMUS

Anatomy and Histology—The thymus is an intrathoracic gland composed of 2 lobes connected by an isthmus Each lobe is made up of lobules that are separated by bands of connective tissue The gland, which at puberty weighs from 10 to 25 gm, is triangular or roughly pyramidal in shape and is separated into two segments the cervical and the thoracic (Fig 187) The upper pole of the cervical segment is

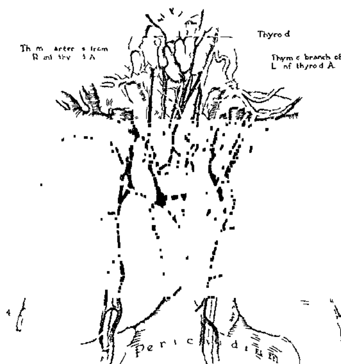


Fig 187—Topographic anatomy and blood supply of the thymus gland (Sloan H E courtesy of Surgery *13* 154 1943)

attached by slender thyrothymic ligaments to the thyroid gland These ligaments contain branches of the inferior thyroid blood vessels This part of the gland is also connected to the trachea the common carotid artery and the inferior laryngeal nerve The thoracic segment lies behind the manubrium and the corpus sterni from which it is separated by areolar connective and lymphoid tissues It extends as far down as the

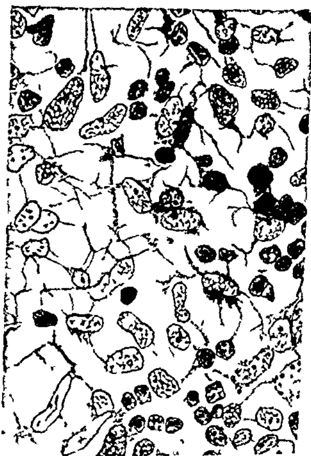
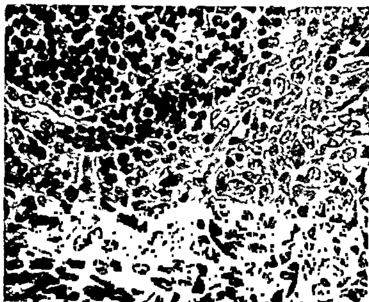
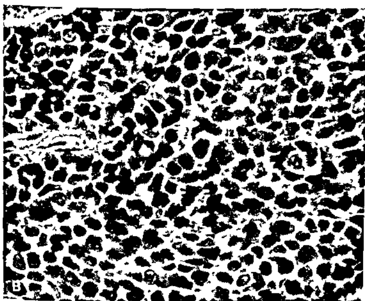


Fig 188—Thymus of human embryo 70 mm showing the epithelial reticulum cell in the early stages of infiltration by lymphocytes (Hammar)

fourth and sometimes the sixth intercostal space In the upper mediastinal space the thoracic segment rests on the right auricle and partially covers the superior vena cava It is attached to both innominate veins but more firmly to the left one The thoracic section also lies close to the mediastinal pleura and the pericardial sac Except for the pericardium to which it is firmly bound its connections with the neighboring structures are tenuous

PLATE II





THYMOMA

A Histological structure of a thymoma made up of reticular epithelial cells and of thymocytes

B Histological structure of a thymoma made up of epithelial reticular cells only

a

Tl

thymic lymphocytes" Cells of a larger size containing poorly defined cytoplasms and ovoid nuclei as well as cells of the reticuloendothelial group are scattered between the thymocytes The medulla is made up of large cells that anastomose and form a so called "epithelial reticulum" It also contains the characteristic Hassall s corpuscles (named after the British physician Arthur Hill Hassall 1817–1894)

The histogenesis and nature of the cells of which the thymus is composed remain unsolved Embryologically the thymus originates as a paired organ from the endodermal epithelium of the third branchial cleft Hammar (who devoted his entire life to the study of this gland in man and the lower animals) and Maximow (who investigated the thymus in tissue cultures) found that at the eighth or ninth week of embryonic life the epithelial reticulum cells are infiltrated by cells from the neighboring mesenchyma (Fig 188) These cells proliferate mature and ultimately assume the morphology and functions of lymphocytes Gradually they squeeze out a large portion of the epithelial cells and form the bulk of the gland which assumes a dual structure comprised of a lymphoid and an epithelial component

This dual concept was contested by Wimwarter and by Stoehr who stated that the lymphocyte like cells are also epithelial in nature It is interesting to note that some observers have even expressed doubts as to the epithelial nature of the epithelial reticulum cells

TUMORS

In the past the thymus gland was regarded as the seat of a variety of intriguing neoplasms No group of tumors has more successfully resisted attempts at interpretation and classification than those of the thymus" wrote Ewing As a result of investigations conducted in recent years the great variety has been considerably reduced Only a small percentage of tumors described as thymic" were found to have originated in the gland many were granulomas erroneously interpreted as thymogenic tumors others were lymphomas and still others metastatic carcinomas The mediastinum which is rich in lymphoid tissue is the starting point of many types of lymphomas including Hodgkin s disease At times these tumors engulf the thymic area incorporating or totally obliterating the gland an occurrence which gives the impression that the tumor is thymogenic That cancer of the lung often assumes a mediastinal form is widely known Minute renal pancreatic and bronchiogenic cancers frequently yield metastases which are chiefly confined to the mediastinum Therefore they

too, were erroneously diagnosed as primary tumors of the thymus Seybold and his associates stated that most of the cases reported as primary thymic tumors by the authoritative pathologist, Symmers, were metastatic from cancer of the lung

Both the paucity of knowledge concerning the potentialities of the thymic cells and the fact that, until recently, investigations had been conducted only on postmortem material have led to erroneous concepts Ewing based his classification on the assumption that all malignant tumors of the thymus originate from the epithelial reticulum cells others believed that tumors may arise from both the epithelial cells and the lymphocytes (thymocytes) Therefore, they divided the tumors into two categories, namely, carcinomas and lymphosarcomas Lowenhaupt listed six types of thymic tumors, stating that each type reproduced ("recapitulated") a phase through which the thymus gland had passed *in utero* Mixed tumors of the thymus, *i e*, "granulomatous" and other varieties, were "isolated"

THYMOMA

Close scrutiny has revealed that the thymus gland yields one incontestably indigenous tumor, which is defined as "thymoma" The term was introduced by Grandhomme in 1901, and although universally adopted, has been interpreted in various ways Crosby, who summarized the literature in 1932, stated "the consensus is that the term 'thymoma' should be used to designate any primary malignant tumor of the thymus This view is contradicted by present day observers

Topography—Gross Appearance—Thymoma is a growth confined to the anterior mediastinal space at the site of the normally situated thymus Because in rare instances the gland is found in ectopic sites, such as the pulmonary parenchyma, the neck, or the pleural surface, the tumor is also found there

Excised thymomas, although generally variable in size, *i e*, from 1 to 10 cm in length and from 1 to 5 cm in width, will sometimes attain much larger proportions They vary in weight from 5 to 150 gm, however, thymomas weighing 300 gm have also been observed Usually they are egg- or pear-shaped (Figs 189 and 197) and are surrounded by a fibrous capsule, which is partially or completely enveloped by normal thymus tissue The outer surface of the growth is humpy but smooth, and its cut surface, which is gray and crumbly, is divided into lobules of various dimensions Each lobule is surrounded by a band of connective tissue (Fig 190) Occasionally cysts of various sizes and shapes are encountered and sometimes deposits of calcium are observed in the capsule

Classification—Microscopic Structure—According to structure, the tumor is classified into three main types



Fig 189 —Thymoma removed surgically



Fig 190 —Cut surface of the thymoma showing division of the tumor into lobules surrounded by bands of connective tissue

1 One type is made up of an almost pure culture of thymocytic round cells, and resembles lymphoma Sparce epithelial reticulum cells are scattered between the thymocytes The tumor is moderately soft and has a rather scant stroma It has been termed "thymocytoma" by some writers, which is probably a suitable designation (Fig 191)

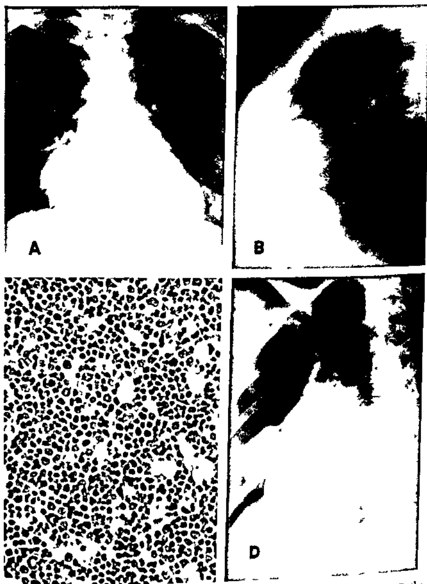


Fig 191 —Thymoma *A B* and *D* posteroanterior lateral, and oblique views *C*, the histology of the tumor made up almost entirely of thymocytes

2 Another type is composed predominantly of the other component of the thymus gland, *i e*, the epithelial reticulum cells These cells (Fig 192) are somewhat elongated, with large vesicular nuclei and sizable nucleoli, arranged in sheets and cords

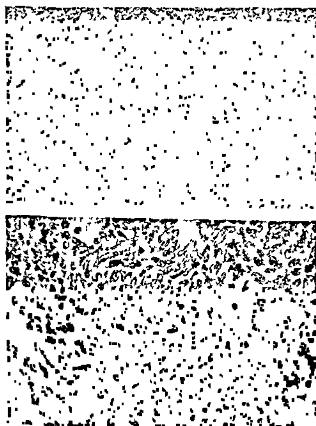
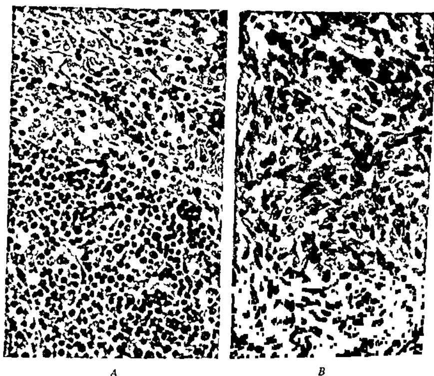


Fig 192—Thymoma made up of epithelial reticulum cells *A* low and *B* high power

3 Still another type is composed of a mixture of both components of the thymus, the epithelial reticulum cells and the thymocytes In the literature this type of tumor has been termed "lymphoepithelioma" This title however, is inappropriate, because it implies malignancy (epithelioma is used to designate carcinoma) The two types of cells are found intermingled in some places and clearly segregated in others (Fig 193)

The last two types imitate the usual structure of the normal thymus gland, *i e*, they are made up of nests of cells separated by thick bands

of connective tissue In the first type the connective tissue partitions are rather rudimentary I have never seen Hassall's corpuscules in such tumors, although some authors have noted their presence Mitoses have not been observed, and generally these tumors are, to all appearances, benign



A B

FIG 193—A, thymoma made up of epithelial reticulum cells and thymocytes (so called lymphoepithelioma of the thymus) B, an area made up almost entirely of epithelial reticulum cells

Thymic Cancer—Malignant Thymoma —The literature contains a considerable number of cases describing carcinoma of the thymus gland But, as stated above, such diagnoses have been regarded critically, if not generally disproved In fact, most observers today are of the opinion that thymoma is invariably a benign neoplasm Seybold and his associates defined thymoma as a slow growing tumor of the thymus gland which has arisen from the epithelial and thymocytic elements of the thymic parenchyma Iverson found thymoma to be a "benign encapsulated neoplasm of the anterior mediastinum arising in the thymus gland and showing various mixtures of cells" A quasi similar view is maintained by Castleman, who emphasized that "the cases reported in

the literature as malignant thymomas with metastases to distant organs do not have the morphologic features pathognomonic of thymomas They are usually malignant lymphomas teratomas or metastatic carcinomas of the mediastinal lymph nodes" In a study of 50 cases diagnosed as thymomas Iverson found that only 27 of these were diagnosed correctly Of the remaining 23 8 cases were found to be thymic carcinomas which resembled seminomas or disgerminomas 5 cases that had been diagnosed as thymomas were identified as mediastinal lymph nodes which showed reactive changes in the follicles simulating Hassall's corpuscles and the remaining 10 cases were comprised of Hodgkin's disease lymphomas and possibly metastatic carcinomas

The presence of a tumor in the neighboring structures *i e* the pleura *the pericardium and the surface of the blood vessels has been interpreted* as an implantation not as a metastasis Indeed embolization (the main feature of a metastasis) has not been observed in expanding thymomas Moreover the tumor did not recur when it was removed before the implantation had taken place

However a spread via the lymphatics was observed by Castleman who maintains—in spite of this—that thymomas are benign He described a case in which a biopsy of an axillary lymph node showed the presence of a thymoma whose extensive spread from the mediastinum into the axilla was revealed only at autopsy In another case reported by him a thymoma had spread over a large part of the right pleura extending through the diaphragm and involving the surface of the liver In still another case the thymoma extended into the abdomen retroperitoneally in addition to which it formed a large periaortic mass

From a study of 19 cases Effler and McCormack concluded that "thymic tumors may be wildly malignant" Binkley and his associates found that 16 of the 21 cases they studied were malignant Qualifying this however Effler found that the tumors are limited in their scope of metastases" and Binkley lent him support by failing to find distant metastases in any of his patients

The crux of the question lies in the interpretation of the term malignancy" Castleman concedes that if implantation extension and invasion of neighboring tissues denote malignancy then some of the thymomas are malignant

The case to be described demonstrates a thymoma with hematogenous metastases

Illustrative Case

Case 20 History—A woman 47 years of age was admitted to the hospital complaining of weakness generalized pain loss of weight and fever Her illness allegedly had started after a fall about 18 *months prior to hospitalization with pain in the left*

side of her chest and shoulder At that time roentgenological examination of the injured parts as well as the entire chest revealed no abnormalities Several months after the onset of the illness she noticed a "bulge in the lower left part of her chest the prominent area of which was pasty Her weakness steadily increased and she began to lose weight She finally became bedridden and was hospitalized

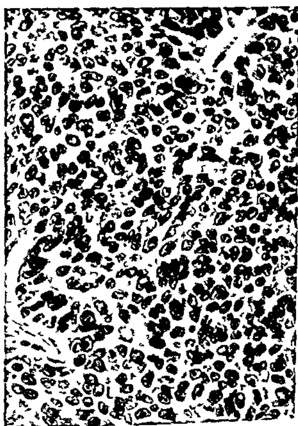


Fig 194—Malignant thymoma

On admission to the hospital she appeared quite ill The left thorax showed a slight doughy prominence of the soft tissue but revealed no evidence of malignancy Roentgenological examination of the chest showed a shadow which suggested the presence of fluid in the pleural cavity (but at autopsy no effusion was found there) The ninth tenth and eleventh dorsal vertebrae and the fourth and fifth lumbar vertebrae showed areas of bone absorption which was attributed to metastases

The patient s weakness progressed and she died a few weeks after she entered the hospital

At autopsy it was found that the anterior mediastinum contained a firm tumor mass identical in appearance with a noninvoluted thymus It measured 10 by 6 cm and extended from the sterno clavicular junction to the xyphoid process overlaying the great vessels of the neck In the lower portion it was divided into two prolongations which spread over the pericardium to which they were firmly adherent At the right border the tumor was ad

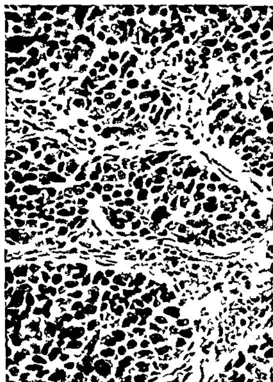


Fig 195—Metastasis to the pleura from the thymoma shown in Fig 194 Note the lobular partition of the metastatic growth imitating the primary tumor

herent to the right middle and upper lobes of the lung into which it penetrated for a short distance The pleura was markedly thickened and contained nests of tumor cells In the region of the tenth rib posteriorly the left parietal pleura contained a small nodule embedded in the pleural leaflet but the left lung and the bronchi were normal A tumor nodule about 5 cm in diameter was found in the lower part of the right lobe of the liver just below the neck of the gallbladder

Comment—The location of the mass in the anterior mediastinum, its shape, and its histological structure (it was made up of the epithelial component of the thymus) were characteristic of a thymogenic neoplasm. Its histological structure, however, was not alone sufficient to label the tumor as malignant (Fig 194).

Although no tumor was present in the lungs, the pleurae contained several neoplastic nodules embedded in dense, fibrous (almost hyalinized) tissue. This pleural growth (Fig 195) showed an insular grouping of the tumor cells surrounded by thick collars of dense, connective tissue almost similar to the pattern of the normal thymus. Now these pleural nodules were possibly produced by implantation of tumor cells, but the hepatic tumor was in all likelihood a hematogenous metastasis. Also, the tumor almost enveloped the large vessels of the neck.

Soutter and his associates stated "It is reasonable to conclude that thymomas are malignant about 50 per cent of the time, and that local invasion into the pericardium and lung or about the great vessels occurs in roughly 1 out of 3. Implants in the chest cavity may be found in a sixth of the malignant tumors, but lymphatic embolic spread is rare"

THYMOMA AND MYASTHENIA GRAVIS

An etiological relationship between thymoma and myasthenia gravis was first suggested by Weigert who found thymomas in patients who had died of myasthenia gravis. He conjectured that the two diseases are related etiologically. Since then, this combination has been observed repeatedly. Bell found 10 thymomas in 56 patients who had died of myasthenia gravis. Blalock found 2 occurrences of myasthenia gravis in 20 thymectomized individuals, Keynes found 41 in 260 excised thymuses, and Eaton and his associates discovered 32 in 206 cases. About 15 per cent of patients with myasthenia gravis had thymomas and 75 per cent who had thymomas suffered from myasthenia gravis. Indeed if an individual with myasthenia gravis reveals a tumor in the anterior mediastinum, the diagnosis of thymoma is virtually certain.

Some observers have stated that myasthenia gravis is due to an alteration in the physiochemical processes that initiate muscular contraction. In theory, the chemical substance is promptly hydrolyzed by the enzyme cholinesterase, which interferes with the chemical substance's prolonged action. According to Constant, the symptom of muscular weakness in myasthenia gravis is due to an interference in conduction from motor nerves to muscles, which is caused by a "thymic factor"

Other observers noted similarities between the symptoms of myasthenia gravis and those produced by the intravenous injection of curare. Therefore, they suggested that the thymus probably secretes a curare-like substance. Still others suggested that myasthenia gravis should

be considered not as an autonomous disease but as a manifestation of dyspituitarism They also conjectured that it is possibly related to an adrenocortical insufficiency

Microscopic studies of the thymus glands that were removed from patients suffering from myasthenia gravis revealed allegedly characteristic features Thus Sloan found germinal centers which are usually absent in normal glands Although he discovered similar structures in acromegaly (in 2 out of 5 patients) in hyperthyroidism (in 5 out of 20 patients) and in Addison's disease (in 3 out of 7 patients) he believes that the quasi constant presence of the germinal centers in the thymus is of significance Castleman and Norris stated that the presence of germinal centers in a thymus associated with involution almost certainly denotes myasthenia gravis

Structural differences likewise have been found in thymomas removed from patients with myasthenia gravis as well as from those without the disease In the latter the thymomas are characterized by a proliferation of lymphoid spindle cell or stromal tissues while changes in the former are evidenced by large pale epithelial cells which are loosely mixed with lymphocytes and often arranged in cords or clusters around vessels (Iverson) In this type of cell Iverson found evidence suggestive of an endocrine function

Thymectomy—The frequent association of thymoma with myasthenia gravis and the probability of an etiological relationship between the two processes prompted Blalock to remove the gland from patients who had this combination Following his successful operations thymectomies were performed on a large number of patients some of whom had thymoma and some others who did not The results obtained thus far remain inconclusive

From a review of 129 thymectomized patients Adams and Allan deduced that 68 of them or 52 per cent showed improvement after removal of the thymoma Kirklin in an analysis of 100 cases reported in the literature found that 64 were either cured or improved by the removal of the thymoma Keynes stated that the treatment of the tumor by primary operation proved to be exceedingly unsatisfactory " but that by applying radiation to the gland prior to the surgical intervention the results obtained by him were very different Thus 15 of his 18 patients are alive today and 3 patients are perfectly well Viets found that in sel

ate

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ual symptoms and in another 25 per cent the results were good so that 65 per cent of selected patients were wholly or in a large part benefitted The operation " Viets continued may not cure the disease but no other form of treatment is followed by such remissions Eaton and

his associates, who also obtained "encouraging" results, concluded that "they (the results) must not be looked on as conclusive evidence that thymectomy is of value in the treatment of myasthenia gravis, since the course of myasthenia gravis cannot be predicted with sufficient certainty to make it possible to say that remission would not have taken place spontaneously in these patients" Other observers recommend thymectomy in the treatment of myasthenia gravis in the presence of thymoma only, still others limited the operation to patients who had not responded satisfactorily to medical therapy and did not show spontaneous remissions

The relationship between myasthenia gravis and thymoma, as well as the effect produced by the removal of the thymoma in patients with myasthenia gravis, is further complicated by the occurrence of myasthenia gravis long after a thymoma has been removed, as illustrated in the following case

Illustrative Case

Case 21 History—The patient was a Negro woman, 38 years of age, married, and a mother of four healthy children During a casual examination at a Board of Health clinic 'the left cardiac border was found 'deformed' and suggested a congenital heart disease ' She was referred to the hospital, where x ray examination suggested a "congenital septal defect, or an auricular aneurysm' However, angiocardiograms disclosed that the abnormality was in reality an extracardiac neoplasm confined to the anterior mediastinum (Fig 196)

At thoracotomy a tumor was found at the site of the thymus gland The tumor (Fig 197), which was readily enucleated, weighed 15 gm, and measured 6 by 4 by 3 cm It was comma-shaped, moderately firm, and had a smooth but humpy surface On its cut surface it was lobulated, and each lobe (of various sizes) was surrounded by a band of connective tissue Histological examination showed that it was made up of cells that resembled the epithelial reticulum cells of the thymus gland The cells were arranged in islands separated by broad rings of dense connective tissue, as noted on gross inspection Within the islands there was virtually no stroma, and the vascularity was moderate There was a scant sprinkling of thymocytes Here and elsewhere a mitotic figure could be seen There were no Hassall's corpuscules present (Fig 198)

The patient was discharged from the hospital and remained well for about 15 months, when she became aware of double vision and weakness in her arms and legs She was readmitted to the hospital, where it was noticed that she could not elevate her eyelids, became hoarse at intervals, and had difficulty in swallowing This condition would last for a few hours, after which she would become normal When given 0 6 gm of qui-

Fig 196 —Thymoma A conventional film and a tomographic film



Fig 197 —Thymoma removed surgically The roentgenological appearance of the tumor is shown in Fig 196

nine by mouth, she would promptly develop weakness, dysarthria, a low voice, and drooping of the upper lids The intravenous administration of 0 5 mg of neostigmine repeated 10 minutes later in conjunction with 0 4 mg of atropine would restore her health It was indeed obvious that she was suffering from myasthenia gravis

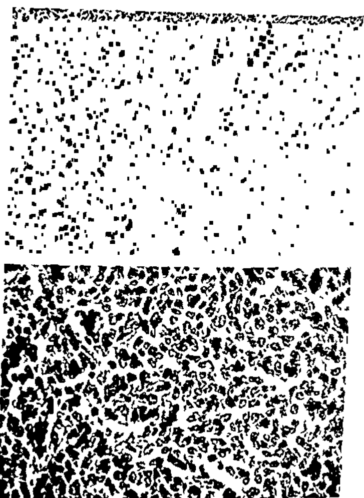


Fig 198 —The histological structure of the thymoma shown in Fig 197

One half gram of neostigmine administrated 3 times daily kept the disease under control although only for short periods On the supposition that subsequent relapses were possibly due to a fragment of neoplastic tissue left *in situ* during the operation the patient was given a course of radiation (2100 r) to the ante

rior and posterior mediastinum without however any change in her condition In spite of the neostigmine therapy (20 mg t i d) she suffered relapses She was readmitted to the hospital during such a relapse She died 24 hours after entry The autopsy revealed no tumor or thymic tissue in the mediastinum or elsewhere in the body

Comment —Gray observed 5 cases of myasthenia gravis which had occurred subsequent to excision of thymic tumor Soutter and his associates reported a case of a 48 year old hypertensive woman who developed myasthenia gravis 22 months after removal of the thymoma Following the removal of a residual gland she had a "favorable response and was alive 8 years later It may be seen in the case reported here that the well circumscribed thymoma was removed *in toto* yet the patient developed myasthenia 15 months later

Thymomas have also been found associated with Cushing s syndrome (Hubble) In view of the relative rarity of this syndrome the finding of a half dozen such cases is probably significant but its meaning remains obscure

Thymoma and the Hematopoietic System —Clinical and experimental observations suggest a relation between thymoma and some types of refractory and aplastic anemias Ross and his associates have described two instances of young women with thymomas who showed refractory anemias Their bone marrows showed a marked hypoplasia of the erythroid elements of the bone marrow associated for a transitory thrombocyto[illegible] the episode of an [illegible] and platelets rem[illegible] medullary hematop[illegible]esis [illegible]as no evidence of [illegible] [illegible]kocytes The authors could not demonstrate a deficiency in any hematopoietic factor and failed to observe a response to therapy with various erythropoietic stimulants They believe that there is an etiological relationship between the thymus gland (or a thymoma) and certain types of refractory anemia They refer to 7 similar cases reported in the literature

It is to be noted however that thymectomy caused no improvement of the anemia in their patients On the other hand in cases reported by Humphreys and Southworth and by Chediak a similar type of anemia was cured (or improved) following the removal of the thymus gland

The literature contains reports of the association of thymoma with aplastic anemia (about 20 cases) which had been treated with ACTH or by thymectomy with contradictory results

Finally thymomas have been found to be associated with agammaglobulinemia As is known this condition is no longer regarded as congenital or sex linked but acquired by adults It is characterized by the total absence or low levels of circulating isoagglutinins and by

absence of antibodies and gamma globulins The patients show virtually no immunological response to challenge doses of antigens This "new disease" was described for the first time by Good in 1954, and since then by several other observers A causal relationship between thymoma and agammaglobulinemia *has not as yet been demonstrated*

Furth and his associates were able to reduce the incidence of leukemia from 80 0 per cent to 9 9 per cent by thymectomy in a high leukemic stock of mice Furth also noticed that although spontaneous leukemia of mice could be inhibited with cortisone (*i e*, by producing lymphoid and thymic atrophy), the complete removal of the thymus has led to a more effective inhibition

Age—Sex—Statistics probably do not reflect the true incidence of thymomas because the material is rather selective and is provided only by clinics that specialize in such cases From a survey of the literature Castleman and Norris gathered the following data which are based on *97 cases of myasthenia gravis with thymoma and 233 nonthymoma myasthenia gravis cases* (Table 21)

Table 21.

	Age							
	0–9	*10–19*	*20–29*	*30–39*	*40–49*	*50–59*	*60–69*	*Total*
Thymomas (number of cases)	—	—	14	28	28	24	3	97
Non thymomas (number of cases)	2	34	91	67	27	8	4	233
Thymomas (percentage of cases)	—	—	14 5	29	29	24 5	3	100
Non thymomas (percentage of cases)	1	15	39	29	11	3	2	100

From Table 21 it may be seen that 14 5 per cent of the cases with thymoma occurred before the age of 30, and none occurred below the age of 20 while in the non tumor patients, 55 per cent occurred before the age of 30, and 16 per cent occurred under the age of 20 Thymomas ... of 30 and 65 and

... seen the

... myasthenia patients with thymoma and those without thymoma Of 59 patients with thymoma, Keynes found 22, or 43 per cent in the male, and 29, or 57 per cent, *in the female* Of 205 patients without thymoma

60 or 31 per cent were males and 145 or 69 per cent were females In a series of 100 cases studied by Eaton and his associates the tumor predominated in the male by an approximate ratio of 2 to 1 However on close analysis the authors concluded that thymomas do not necessarily have a tendency to develop in the male" Keynes stated that "tumor formation is a disease of the older individual with myasthenia

DIAGNOSIS

Thymoma is a slow growing neoplasm that rarely exceeds the size of a hens egg although there have been cases reported where the tumor [illegible] has been found that the usual size [illegible] A diagnosis has probably never [illegible] such as widening of the area dullness or flatness of the upper mediastinum dyspnea cough or cyanosis The tumor usually surrounded by normal thymic tissue lies between the rigid sternum and the resilient heart and large vessels The latter recoil under pressure of the growth without however producing serious symptoms

Symptoms appear when the tumor attains considerable size and invades or implants itself on adjacent vital structures i e the heart or large veins The superior vena cava syndrome which is caused by the wrapping (or rarely the invasion) of the wall of the vein has been observed in many cases This symptom details of which are described in Chapter 5 is a late manifestation In its early stages the tumor usually can be seen on x ray films

The roentgenological examination should be performed with diligent care The conventional anteroposterior films alone are not always sufficient to reveal the new growth which may be hidden behind the shadow of the heart or behind other structures Lateral and oblique views are essential It should also be remembered that the thymoma may not always be found in the anterior upper mediastinum where it is usually present but it may be lodged further down close to the diaphragm

An anterior mediastinal tumor when found in a patient with myasthenia gravis should be diagnosed as a thymoma until proven otherwise Conversely in the absence of myasthenia gravis a diagnosis of either lymphoma enlarged lymph nodes a terato-dermoid or a metastatic carcinoma should be considered first

THYMIC CYSTS

The pathogenesis of the thymic cyst is as uncertain as the many other aspects of the gland itself In former years some clinicians believed that its inception was due to either syphilis or a pathogenic infection others

thought that the large thymic cysts were very likely congenital in origin, arising from remnants of the branchial clefts

Thymic cysts are lined by a squamous, cuboidal or flattened epithelium, and are surrounded by a thick capsule which, in turn is enveloped by normal thymic tissue Sometimes they attain a voluminous size as evidenced by a case reported by Pixley, Piper, and Bowers who removed a cyst containing 1,000 cc of yellowish brown opalescent fluid This particular mass was discovered in the anterior mediastinum of a male patient 28 years of age, during a routine x ray examination Except for a moderate shortness of breath on exercise and an occasional substernal burning sensation when straining or lifting the patient was asymptomatic

Generally the symptoms depend upon the size and position of the cyst However, if one is to judge from the above mentioned case even large cysts may yield few symptoms It is possible that the resilient cyst unlike the firm thymoma, is incapable of compressing the large veins or the atrium When the cyst becomes enlarged, symptoms appear because of the accumulation of fluid or blood which normally is present in small quantities These symptoms consist of a tightness or a pain in the chest Large cysts particularly when situated high in the mediastinum are apt to cause hoarseness and difficulty in breathing

While the roentgenological examination can ascertain the presence of a density in the mediastinal space as well as its size and position the diagnosis is made at an exploratory thoracotomy A cure is effected by means of surgical extirpation

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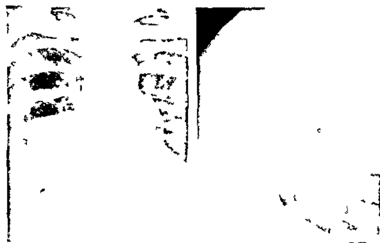


Fig 199—Dermoid in an ad lt

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Fig 199—Dermoid in an adult

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Structure—Mediastinal terato dermoids grossly and histologically resemble the same type of tumors found in other localities They also assume a predominantly solid or cystic structure The most common form of the cystic tumor is the epidermoid cyst (simplified teratoma) which contains hair follicles sebaceous and sweat glands (Fig 199) cellular debris fat and hair Occasionally it is traversed by solid ridges that form pseudo partitions The tumors vary greatly in size at times attaining the dimensions of a large grapefruit The wall is fibrous and as a rule is lined with stratified squamous epithelium (rarely with columnar or cuboidal epithelium) Like the solid teratoma the cystic

Chapter 18

Terato-dermoids

Definition.—Terato dermoids are congenital malformations which are classified as (1) dermoid cysts, presumably composed of tissues from one germinal layer, and (2) teratomas, composed of three germinal layers However, on close examination it seems unwarranted to divide these structures into sharply defined entities because it has been found that the allegedly monodermal malformations frequently contain tissues from more than one embryonic leaflet Also, the opinion that they are either entirely cystic (dermoids) or diffusely solid (teratomas) has been disproved Solid areas are present in cystic tumors, and conversely, cysts are found in the seemingly solid growths It is considered more appropriate to designate them as 'terato dermoids,' which may be either predominantly cystic or predominantly solid It is perhaps of greater significance to classify them as the mature, or benign type and the immature (embryonic) type, which is often malignant

Histogenesis and Location—The histogenesis and mode of formation still remain unsolved It is surmised that they may arise from totipotent primitive cells (undifferentiated precursors of the germ cells), which, under certain conditions, produce a chaotic structure that occasionally becomes malignant Willis wrote, 'At least a dozen different histogenetic hypotheses based on no other than their author's imagination have been advanced and endlessly debated"

Terato dermoids occur predominantly in the testes, the ovaries, the sacrococcygeal region, and the mediastinum They are also found in the brain and in the retroperitoneal and intrapericardial regions The prevalence of these cysts in the gonads has been explained on the supposition that the totipotent sex cells, or their predecessors, possess features that predispose them to the formation of this strange type of neoplasia

Mediastinal

The occurrence of terato dermoids in the mediastinal space has been explained in various ways One group of investigators has attributed their incidence to the presence of aberrant sex cells in the mediastinum, another group has maintained that it is due to an abnormal development of the third and fourth branchial arches It has been conjectured that the 'monster' cells separate from the arches at this point and are carried

into the thorax with the normal descent of the heart and great vessels Jacobs epitomized this concept as follows "During the early embryonic period the anlage of these tumors is in the cervical region along with the lungs heart and thymus They move into the thorax along with these organs This is suggested rather strikingly in a number of cases but particularly in the case of Colleburg who found band like connections from the posterior part of a large tumor situated in the right lower anterior mediastinum that extended upward to the lower edge of the right lobe of the thyroid He was able to trace a branch of the inferior thyroid artery into this band along with some fibers of the sterno thyroid

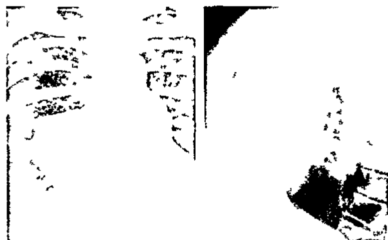


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teratoma is apt to undergo a malignant transformation However, the tendency of the cystic type to become malignant is much less pronounced The ratio is about 1 to 3

The predominantly solid teratoma—sometimes called the "unorganized teratoma," in contradistinction to the "organized teratoma" in which rudimentary organs are formed—is composed of chaotically arranged neoplastic tissue of bidermal or tridermal origin that lacks the propensity *to form organs* *The neoplasm usually* is made up of solid nests of squamous epithelium, connective tissue, cartilage, smooth and striated muscle, glia, respiratory, intestinal, *and renal epithelium, teeth, bone,* and hair The tumor may remain benign indefinitely, or it may undergo a malignant transformation limited to the epithelium

Location.—Terato-dermoids are located in the anterior mediastinal space behind the sternum and often lean toward one side of the thoracic cavity *Occasionally they extend into the upper mediastinum and pro*trude into the neck Of 15 cases observed by Harrington, 6 projected *into the left side, 6 into the right side, and 3 projected into both sides of* the cavity In 2 cases it was confined to the anterior and superior mediastinal spaces and extended into the neck

Age.—Because the tumors are congenital, the patients' ages at the time the symptoms first appeared are given In the above-mentioned series outlined by Harrington, the youngest patient was 17 years old, and the oldest was 59 On the average the symptoms appeared at the age of 32

Sex.—*The incidence of terato-dermoids is almost equally distributed* between the sexes Of 177 cases collected by Rusby, 91 occurred in men and 86 in women In Harrington's terato dermoid cases 12 were women and 3 were men Malignant tumors were observed predominantly in the male following a ratio of 8 to 1

Malignant Transformation.—In 191 cases of dermoid cysts and teratomas of the mediastinum reported by Hedblom, 17, or 8 9 per cent, were malignant *In 1936 Houghton found 24 additional cases in the literature,* to which he added 1 of his own Lappily, in a series of 246 cases, found that 28, or 11 4 per cent, were malignant, Heuer and Andrus found malignant changes in 5 out of 13 cases, and Blades discovered malignancies in 6 out of 20 cases

From a review of 200 reported cases, Fox and Hospers estimated that about 55 per cent were simple dermoids, 25 per cent were complex, benign dermoids, and 20 per cent were *malignant dermoids* In most instances it was a single element—the epithelium—that became malignant, but in *a few cases two elements underwent* a malignant metamorphosis In the 2 cases of solid teratoma reported by Fox and Hospers, 1 contained elements derived from at least two germinal layers It consisted of localized, adenocarcinomatous, and sarcomatous changes The sarcoma

had invaded the lymph nodes the lungs the liver the spleen and the bone marrow

Houghton's case concerned a man 22 years old whose symptoms of mediastinal obstruction had begun 10 months before hospitalization He had apparently died from mechanical strangulation that had been caused by pressure The autopsy revealed that there was a solid teratoma weighing 1 590 gm in the mediastinum with metastases to the pleura the lungs the liver the vertebral column and a single peribronchial lymph node There was also atelectasis of the right lower lobe and a hydrothorax on the right side The teratoma was of the complex type with derivatives from all 3 embryonic layers

Chorioepithelioma —Chorioepithelioma is a subvariety of the embryonal adenocarcinoma In the female it arises from the epithelium of the chorionic villi and in the male it originates from the germinal (undifferentiated totipotential) cells which are found in teratomas Formerly whenever a teratoma with chorioepitheliomatous changes was found in the mediastinum it was regarded as a metastasis from the testes even though there was no tumor in the gonads This was based on the observation that (1) chorioepitheliomas after having metastasized to distant organs heal spontaneously (the regression of a chorioepithelioma in the female has frequently been observed) and that (2) testicular teratomas are easily overlooked because they are usually of a very small size Although these observations have been proven to be correct in the majority of cases there are instances on record where the mediastinum was found to be the primary seat of the growth It is believed that the mediastinal chorioepitheliomas like the retroperitoneal chorioepitheliomas which arise from aberrant testicular tissue (the so called "abdominal testes") also arise *in loco* from aberrant testicular cells (the so called "mediastinal testes") It is well to point out that while aberrant ovarian tissue has been identified in the mediastinum aberrant testicular tissue has never been found there It can be seen that the origin of chorioepithelioma in a mediastinal teratoma remains "a riddle wrapped in a mystery inside an enigma"

The characteristics of testicular teratomas *i e* their small size their metastatic propensities and their tendency to regress spontaneously after a wide metastatic spread have prompted pathologists to study cases with the utmost care As a result they have reached the conclusion that chorioepitheliomas do originate in mediastinal teratomas and that they occur almost exclusively in the male Of all the cases thus far reported there were only two or three that occurred in a female

Duration —In cases of benign teratoma the illness may be protracted while in cases of malignant teratoma the course is rapid In 6 of Schlumberger's patients death occurred 5½ months after the onset of the symptoms His youngest patient was 19 years old and his oldest was 29

years of age Houghton estimated that the disease may last from 1 to 2 years

Clinical Manifestations

Onset of symptoms—Although terato dermoids are congenital tumors they rarely manifest themselves before puberty From Table 22 it may be

Table 22

(Rusby)

Age (years)	*No of Cases*
0–9	17
10–19	27
20–29	68
30–39	37
40–49	11
50–59	13
over 60	1

seen that in only 10 per cent of cases did symptoms appear in the fifth decade of life while in 40 per cent the symptoms became apparent in the third decade Of 10 patients of military age who had benign teratomas Schlumberger found 2 that were free of symptoms In each case the disease had been discovered on a routine roentgenological examination It has been suggested that hormones may be responsible for the awakening of this dormant congenital abnormality However in most instances the appearance of symptoms followed a pulmonary infection which simultaneously had involved the teratoid It also has been noticed that the onset of symptoms coincided with a malignant transformation Trauma too was found to be a predisposing factor

Pain—The earliest complaint is pain in the upper mediastinum limited however to the area occupied by the teratoid It is probably related to a concomitant pleuropneumonitis to a great extent When the growth is situated in the upper mediastinal space it is apt to encroach on the brachial plexus and to simulate the symptoms of the superior pulmonary sulcus tumor These consist of pain in the shoulder radiating down the arm along the ulnar side numbness and tingling in the hand and fingers muscular weakness paresis and Horner's syndrome Teratomas that are located in the upper mediastinum also are apt to induce a superior vena cava syndrome

Cough—Cough is more pronounced when the patient is in a recumbent position It is usually dry and hacking but at times it is productive of a gelatinous sputum which may contain hair Gross inspection of the sputum is an important procedure as it may provide an early clue

Hemoptysis has rarely been observed but blood streaked sputum has frequently been noticed A tumor that is situated predominantly on the left side may cause hoarseness by pressing on the recurrent laryngeal nerve or on one of its branches

Dyspnea—In the early stages of the disease dyspnea is evident only on exertion But such eventualities as a pulmonary infection an increase in the size of the tumor or the compression of a large vascular trunk will induce constant and crippling shortness of breath which at times is asthmatic in character

Bronchostenosis—Bronchopleural Fistula—An expanding terato dermoid may compress one or two bronchi and cause stenosis of the bronchial lumina sometimes it completely obliterates them The segment of the lung that is furthest from the obstruction becomes infected with pathogens which may produce pneumonitis an abscess and bronchiectasis

The pleural cavity too becomes involved by way of a bronchopleural fistula It has been observed that a neglected teratoma may lead to an empyema Occasionally the empyema is caused by a spontaneous rupture of the cyst into the pleural cavity

Diagnosis—The appearance of characteristic symptoms usually is a sign of an infection or of a malignant transformation of the tumor Therefore it is of the utmost importance to detect the disease in its presymptomatic stage It is difficult to diagnose a terato dermoid because the symptoms resemble those presented by other intrathoracic neoplasms Inspection often reveals a bulging of the affected hemithorax particularly when the tumors are found in the young On percussion the anterior aspect of the chest is flat while the posterior aspect is hyperresonant A prompt search for a terato dermoid should always be instituted whenever symptoms of intrathoracic pressure occur in young patients

In former years clinicians attached great importance to the gelatinous expectoration which they considered a characteristic sign They diligently searched for hair and it has been reported that the discovery of a single hair sufficed to establish a diagnosis

Whenever a teratoma is discovered in the mediastinum the possibility that it may contain chorioepithel omatous elements should be considered Neoplastic chorionic tissue like normal chorionic tissue (*i e* chorionic villi in pregnancy) manufactures a luteinizing hormone which is detected by the Aschheim Zondek or Friedman tests While a negative test does not exclude the possible presence of such elements (which may be due either to the insufficient production in the amount of hormones or to necrosis of the trophoblastic elements) a positive test is of diagnostic importance In the presence of chorioepithelioma the prolan excretion is 10 to 500 times greater than that observed in a normal pregnancy Tests of from 01 to 1 cc are often sufficient to produce

positive reaction The generally low titers for estrogens in the urine nd in the blood, as compared with the much higher titers associated with normal pregnancy, is an important diagnostic feature

Roentgenological Examination —The use of roentgen rays is of great mportance in diagnostic procedures, particularly in cases where rudi nentary organs or structures (teeth) are seen Generally the presence f a well-defined, roundish or oval mass that is predominantly unilateral strongly suggestive of a teratoma Mediastinal teratomas often show reas of calcification However, similar changes also can be seen in hymogenic tumors and in adenomas

Therapy —The growth should be removed surgically whenever possible

Illustrative Case

Case 22 History —The patient, a white married woman 31 years of age was admitted to the Morrisania City Hospital with a diagnosis of subacute bacterial endocarditis and septicemia She had been in perfect health until she had given birth to her first child at the age of 23 She then became aware of weakness, flatulence, and fleeting pains in the joints Two years later, at the age of 25, her tonsils were removed, but the fleeting articular pains did not subside Two years following the tonsilectomy she began to complain of malaise, she also suffered from intermittent fever A murmur was heard at the apex of the heart, and it was then, at the age of 27, that the diagnosis of subacute bacterial endocarditis was made for the first time One blood culture was sterile She was given penicillin for 10 days, and her temperature returned to normal On roentgenological examination of the chest a well defined area of density was revealed in the region of the pulmonary artery, the nature of which was not understood

Subsequently, she developed intense dyspnea, tired very easily and found it necessary to spend a great deal of time in bed

and 201)

At the age of 31 the malaise and fever recurred, and on a few occasions she had chills She was treated with penicillin for a period of 10 days, with no effect

When she was admitted to the hospital, she did not appear to be ill Her temperature was 100° F. The urinalysis showed no abnormalities There was a normocytic, hypochromic anemia, and the leukocytic count showed 17,000 white cells per cu mm, 90 per cent of which were of the polynuclear series The Wasserman reaction and the blood cultures were negative Her temperature oscillated between 100° and 102° F. The diagnosis

of subacute bacterial endocarditis was once again made Although she was given large doses of penicillin her temperature did not return to normal

On the seventeenth day of hospitalization she suddenly became dizzy and moments later she died



Fig 200 —Teratoma A roentgenogram taken n 1948 B taken in 1951

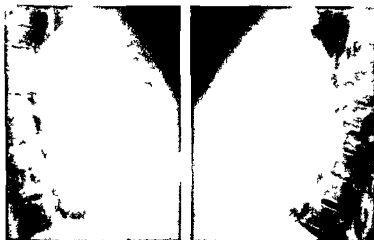


Fig 201 —R ght an l left l teral v ews of roentgenogram taken in 1951

Autopsy —At the autopsy a large distended fluctuant cystic tumor was found firmly adherent to the sternum It covered the heart and the great vessels displacing them to the right The tumor which was twice the size of the heart was firmly attached

to the right ventricle and the left lung When the cyst was opened it was found to contain a thick, nonodorous greenish oily material It also contained inspissated grumous material and a clump of hair The wall of the tumor, measuring from 5 to 8 mm in thickness was shaggy and irregular There was nothing remarkable in the appearance of the pulmonary vessels or the lungs

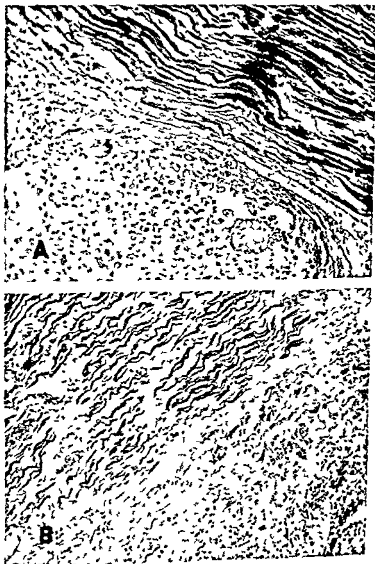


Fig 202—*A* cyst at the border of the myocardium *B* abscess in the myocardium

External examination of the heart was negative A minute thrombus was attached to the endocardium in the apical region of the right ventricle, and beneath the thrombus there was a focus of endocarditis The myocardium contained an abscess filled with pus Abscesses were also found in the right ventricular wall, in the apical portion of the left ventricle, and in the apical portion of the interventricular septum (Fig 202)

Microscopically the wall of the cyst contained areas of squamous epithelium, hair follicles, muscle fibers sebaceous glands, and many small abscesses (Fig 203)

The diagnosis was dermoid cyst of the anterior mediastinum, communicating with abscesses in the myocardium



Fig 203—Sebaceous glands in the wall of the cyst

Comment—In this case, except for the unusual infection of the myocardium the manifestations of the dermoid cyst were rather characteristic The symptoms appeared in the third decade of the patient's life and were initiated, in all likelihood, by an infection The dyspnea was caused by pressure of the dermoid cyst on the heart and large thoracic vessels This case illustrates an example of the co-existence of two diseases in which the symptoms of one disease eclipsed those of the other The clinician's attention was diverted from the presence of a neoplasm by the more dramatic manifestations of the superimposed infection The autopsy findings of a dermoid cyst came as a complete surprise to the medical staff



FIG 204—Terato Dermoid Angiogram *A* lateral angiography showing filling of the right heart and of the pulmonary arteries also the retrosternal location of the tumor The superior vena cava the right ventricle, the pulmonary conus and the pulmonary arteries show deformities *B*, shows displacement of the superior vena cava and the compression of the ventricle and of the pulmonary conus The left pulmonary artery is elevated and pushed medially, the right heart is filled *C* shows opacification of the left heart and of the aorta also deformity of the ventricle and anterior displacement of the ascending aorta The extracardiac position of the mass is evident

The use of angiography as a means of diagnosis in cases of mediastinal tumors is discussed in Chapter 8

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Chapter 19

Neurogenous Tumors

NEUROGENIC tumors may arise in the following structures

1 The peripheral nerves
2 The sympathetic system
3 The chromaffin system

It is desirable to begin with a brief review of the anatomy of these structures

ANATOMIC CONSIDERATIONS

Peripheral Nerves —The nerve cell is provided with several short fibers known as "dendrites" and one long fiber known as the "axis cylinder (axon neurite or nerve fiber) Each axis cylinder is enclosed in a tube like structure called "neurilemma" which is made up of a syncytium of cells Since these cells were identified for the first time by Schwann they were named after him

A nerve trunk is made up of innumerable fascicles or bundles of axis cylinders Each fascicle is surrounded by a ring of connective tissue called "epineurium" The epineurium gives off fibers defined as 'endoneurium' which insinuate themselves between individual axis cylinders The entire nerve trunk is surrounded by a collar of connective tissue termed perineurium (Fig 205)

The nerve cells as well as the Schwann cells of the neurilemma are derived from the primordial cells of the neural crest which is an aggregation of cells gathered in the angle between the medullary tube and the surface ectoderm In the early stages of embryogenesis these cells move away from the neural crest of the medullary tube They then spread out to the intramural plexuses of the viscera and along the segmentary visceral rami of the anterior spinal nerves i e the dorsal root ganglia and the sympathetic and chromaffin systems The latter is confined chiefly to the medulla of the adrenal gland (Fig 206)

The Sympathetic and the Chromaffin Systems —The stem or primordial cells of the nervous system known under the names of "neurocytes" "neuroblasts" or sympathogonia resemble the lymphocytes of the circulating blood They give rise to two systems (1) the sympathetic and (2) the chromaffin

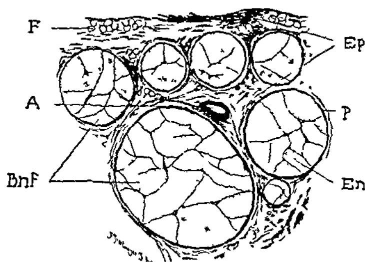


Fig. 205.—Cross section of a human nerve. Ep, epineurium; P, perineurium; En, endoneurium; Bnf, bundles of nerve fibers; A, artery; F, fat cells. (From Histology edited by R. O. Greep, 1954, courtesy of Blakiston Div., McGraw-Hill Book Co.)

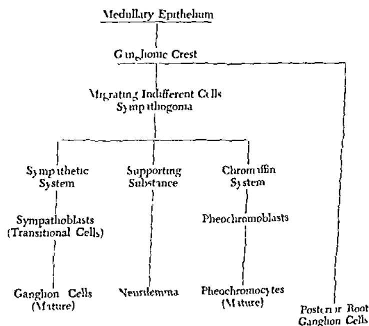


Fig. 206.—Diagram illustrating the development of the cells of the nervous system.

The sympathetic system is formed by differentiation of the neurocytes into so called "sympathoblasts" which in turn differentiate into ganglion cells that are no longer capable of further differentiation

The chromaffin system is formed by the differentiation of the neurocytes into pheochromoblasts which in turn differentiate into pheochromocytes Like the ganglion cells the pheochromocytes are the last generation and are no longer capable of further differentiation (Fig 207)

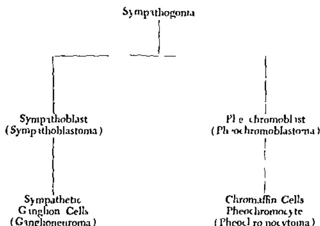


Fig 207 —Diagram to show the development of tumors from cells of the sympathetic nervous system (Bielchowsky)

The peripheral nerves as well as the cells of the sympathetic and chromaffin systems are potential sources of the origin of benign and malignant tumors within the thoracic cavity

TUMORS OF PERIPHERAL NERVES

Neurinoma—Neurilemoma—Schwannoma —Observers disagree about the particular component of the nerve from which the tumor arises One school of thought supports the theory that the neoplasm starts in the connective tissue *i e* the perineurium the epineurium and the endoneurium of the nerve trunk others believe that it originates in the neuroectodermal Schwann cells which form the neurilemma The preponderance of evidence however points toward the second source hence the terms "neurinoma" "neurilemoma" and "schwannoma"

Intrathoracic Neurinoma —Within the thorax neurinoma originates either in the posterior root of the spinal nerve or in an intercostal nerve As a rule the tumor starts in the paravertebral gutter *i e* in the poste-

rior mediastinal space In 18 proven and 3 unproven cases studied by Kent and Blades, 19 tumors were found in the posterior mediastinal space, and in 101 reports obtained from the literature, only 2 tumors were found in the anterior mediastinal space Indeed, in any case where a tumor is found in the posterior mediastinal space, there is a strong presumption that it is neurogenic in origin

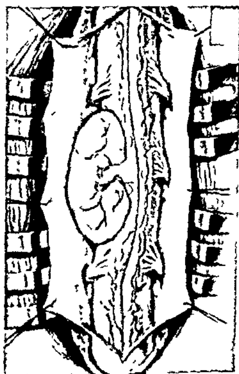


FIG 208—Neurinoma (neurilemoma) The kidney-shaped tumor is circumscribed and encapsulated It compresses the cord

Generally the tumor is benign and is encapsulated by the perineurium 'The capsule,' wrote Masson, "surrounds the tumor everywhere at the spot where the nerve penetrates into the tumor, and there, the perineurium of the nerve continues as a capsule" The tumor is solitary, somewhat round or spherical in shape, yellow, gray, or pink in color, and may attain considerable size, i e, from 10 to 15 cm in diameter (Fig 208)

Histology—The histological picture, in intrathoracic neurinoma, is characteristic because of the two aspects it assumes These are described as Antony A and Antony B types (after the pathologist who pointed out these features) The Antony A type shows an orderly arrange-

ment of the Schwann cells, with (1) the nuclei lined up in parallel rows, (2) blunt, anastomosing ends and (3) ramifications from neighboring cells. These form a syncytium known as the "palisade" or regimented pattern. Although the pattern is not a constant feature, nevertheless it is considered characteristic.

In contrast to the Antony A pattern which produces a firm structure, the Antony B type forms a soft reticular structure that is made up of a loose meshwork of fine collagenic fibers with spaces or cyst like lacunae. Some observers consider this process to be a result of degeneration, whereas others feel that it is but another aspect of the tumor. Both patterns are often found in the same tumor and even in the same section (Fig 209).



Fig 209.—The histological structure of neurinoma. The Antony A type (orderly regimented nuclei lined up in parallel rows) is illustrated on top of the picture; the Antony B type (reticular structure resembling cyst like lacunae) is seen in the center of the photomicrograph and in the lower left corner.

Illustrative Case

Case 23 History —A 30 year old male was admitted to the hospital with the diagnosis of tumor of the lung The growth had been discovered 10 years before during a routine examination of the chest (Fig 210) Periodic examinations showed that it had been steadily increasing in size However it had produced no symptoms The patient had been rejected for military service because of the intrathoracic growth



Fig 210 —A mediastinal neurinoma B picture taken seven years later C and D show the lateral and oblique views of the tumor

Examination revealed ...
tress The ...
in the lower ...
were found elsewhere

Roentgenological examination of the thorax disclosed an area of increased density which was ovoid in shape and measured 12 cm in length 9 5 cm in width and 12 cm in depth It was situated in the paravertebral region (Fig 210) of the medial portion of the right posterior mediastinum The heart was displaced to the left A pneumothorax was induced which showed that the tumor was extrapulmonary The diagnosis was neurinoma of the medial portion of the right mediastinum

Hourglass Neurinoma —Hourglass neurinomas are tumors that are made up of two components namely intraspinal and extraspinal They are bridged by a constricted stalk that extends through the root canal or between the laminae (Fig 211) Although the intrathoracic segment of the growth usually exceeds the intraspinal portion in size in most instances the early symptoms are referred to the intraspinal portion This is obviously due to the sensitivity of the cord to minimal pressure

Intrapulmonary Neurinoma —As stated above the posterior mediastinal space is the customary seat of an intrathoracic neurinoma In the following case the neurogenous tumor was within the lung proper

Illustrative Case

Case 24 History —The patient was a girl 16 years of age A routine roentgenological examination showed a round area of density about 3 cm in diameter at the level of the anterior portion of the posterior segment of the right upper lobe It was surrounded by normal lung tissue was separated from the mediastinum and showed no calcification The remaining portion of this lung as well as the left lung, showed no abnormalities (Fig 212 *A*)

The patient's past history was negative Her mother had died of tuberculosis when the girl was 6 years old Repeated Mantoux tests and chest *x* rays given after her mother's death were negative However the year following her mother's death the Mantoux test became positive The patient was not seen again for several years but at the age of 15 came in one day for a routine chest *x* ray examination During the intervening years she had been in good health

The physical and laboratory examinations were noncontributory The round dense shadow in the lung discovered with the *x* rays was tentatively diagnosed as a tuberculoma and the patient was referred to the Presbyterian Hospital New York City for an exploratory thoracotomy

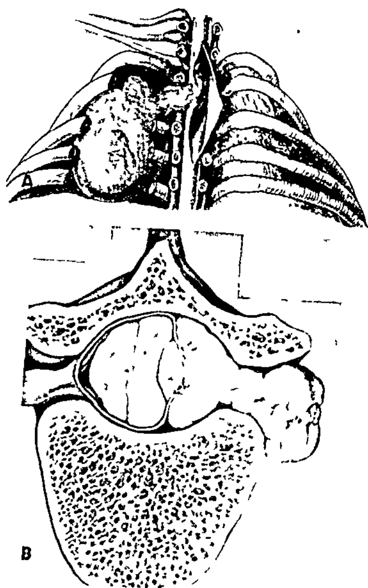


Fig 211—*Hourglass shaped neurinoma* *A* the intrathoracic component of the growth is voluminous by comparison with the intraspinal *B* the intraspinal and extraspinal components are about equal in size (*B* courtesy The Ciba Collection of Medical Illustrations Vol I)

The operation revealed a hard encapsulated mass 3 cm in diameter It was somewhat round smooth and glistening and was attached posteriorly to the terminal bronchus of that segment. The pathological diagnosis was neurinoma (neurilemoma) (Fig 212 B) A tissue culture of the removed tumor

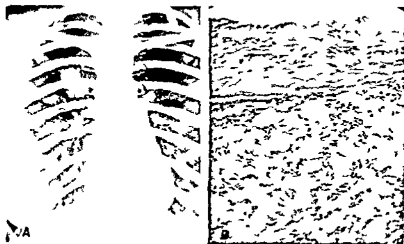


Fig 212—A roentgenogram showing a neurinoma within the pulmonary parenchyma B the histological structure of the tumor (Antoni A type) The dense fibrous capsule of the tumor is seen on top of the photomicrograph

performed in Dr Stout's laboratory corroborated the histological findings Three more cases that were reported in the literature as neurinomas of the lung lacked the typical histological picture of the neurogenic tumor Two of the cases involved the pleura and one was a pedunculated pleural mass (Lane *et al*)

Malignant Neurinoma—Although the existence of a malignant neurinoma has been denied by many observers such cases have been reported The malignant neurinoma is a metastasizing tumor derived from the Schwann cells Like the benign variety it displays the palisade pattern of the Schwannian nuclei

Sainton and Lehrmite reported a case of an adult male who had a neurinoma on the dorsum of his foot The tumor had developed on a branch of the sciatic nerve After it had remained asymptomatic for 30 years similar tumors appeared on the same nerve trunk on the buttocks and on the leg The authors believed that the newly developed neurinomas were metastatic from the 30 year-old growth which had become malignant Ackerman and Taylor observed 4 cases of neurinoma which they thought could be designated as malignant Three of the patients

had clinical stigmata characteristic of von Recklinghausen's disease It is the opinion of many observers that malignant neurinomas occur only in patients with neurofibromatosis

Neurofibroma —The terms "neurofibroma" and "neurinoma" have been used interchangeably, but, aside from a common histogenesis (from the neuroectodermal Schwann cells), they are entirely dissimilar Unlike the neurinoma, the neurofibroma is not encapsulated It grows diffusely engulfing the periepineural connective tissue as well as the neurilemma *Histologically* it lacks the regimented palisading of the Schwannian nuclei that is so characteristic of the neurinoma It is composed of irregularly interlaced spindle cells, with myelinated and nonmyelinated neurites—which are often oriented in relation to the axon cylinders—running through the tumor It is particularly interesting that, unlike the solitary neurinoma, the neurofibroma is part of a multiple neurofibromatosis (von Recklinghausen's disease) which is known to have hereditary and familial tendencies' Also, it is noteworthy that the neurofibroma undergoes a malignant metamorphosis in a considerable percentage of cases Stout found metastases in 18 of the 19 cases that he analyzed

In the majority of cases, it has been found that neurofibromatosis also affects the skin and the subcutaneous tissue, forming tumors of various sizes and shapes, some of which appear as mere freckles The bones and the viscera, also, were found to be involved in a number of cases

Intrathoracic Neurofibroma —In the thoracic cavity, neurofibroma arises either in the paravertebral sympathetic trunks or in the intercostal nerves from the Schwann cells, forming solitary or multiple tumors (Fig 213) The latter often display striking clinical manifestations The solitary intrathoracic tumors remain unnoticed until they attain a considerable size, at which time they begin to cause pressure on vital organs or structures They also produce symptoms after they undergo a malignant transformation

Whenever a tumor of neurogenous origin is found in the posterior mediastinal space, a search should be made for stigmata of neurofibromatosis Conversely, in any case of neurofibromatosis, the thoracic cavity should be investigated for the possible presence of a neurogenous growth

Intrathoracic Meningocele —Meningocele is another condition which accompanies neurofibromatosis and is confused with intrathoracic neurofibroma Meningocele is a cystic structure, the walls of which are made up of the dura and the contents of cerebrospinal fluid The "cyst" results from a herniation of the dural envelope of a spinal nerve through a congenital defect in the bodies and foramina of the vertebrae (Neurofibromatosis is characterized by numerous congenital abnormalities)

Welch and his associates, who reported a case of a successful removal of a meningocele, pointed out that it arises as a lateral structure, usually

projecting through the intervertebral foramina It then passes anteriorly between the ribs projects paravertebrally into the thoracic cavity and pushes the posterior parietal pleura forward The course of the intrathoracic meningocele is like that of the dumb bell neurogenic tumors which grow inside the spinal column and the thoracic cavity Roentgenologically they cast a picture similar to a neurofibroma with which they usually have been confused The nature of the lesion is discovered



Fig 213 —A pulmonary t mor in a case of ne rofibromatos s

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observed with the x rays In the past surgical intervention invariably led to death (caused by leakage of cerebrospinal fluid into the pleural cavity and by empyema) Recent reports however have described the successful removal of intrathoracic meningocele

TUMORS OF THE SYMPATHETIC NERVOUS SYSTEM

Sympathoblastoma (Neuroblastoma) —In the preceding section it was pointed out that the primitive or formative cells of the sympathetic system *i e* the sympathogonia differentiate into sympathoblasts which in turn differentiate into ganglion cells It was found that each of these may give rise to tumor formation namely (1) sympathogonia produce sympathogoniomas (2) sympathoblasts produce sympathoblastomas and (3) ganglion cells produce ganglioneuromas

Seat.—The primary seats of these tumors are the medulla of the adrenals and the abdominal, cervical, pelvic and thoracic sympathetics. The *adrenals are the most frequently involved*. The tumors metastasize widely to the viscera and the skeleton. They occur predominantly in infancy.

Intrathoracic Sympathoblastoma.—In 1937 Scott and Palmer culled from the literature 37 cases of tumors of the sympathetic nervous system outside of the adrenal medulla. In a series of 48 cases of intrathoracic *neurogenic tumors*, *Ackerman and Taylor found 3 neuroblastomas (sympathoblastomas).*

In 1943 Sailer reported a case of mediastinal sympathoblastoma in a woman 65 years of age and tabulated 8 cases from the literature. In his own case the tumor was found in the anterior mediastinum beneath the pericardium. *It probably arose from the sympathetic rami of the* deep cardiac plexus.

Anderson and Shennan reported a case where the tumor originated at the apex of the right lung and was attached to the second and third ribs as well as to the sides of the dorsal vertebrae. In the case observed by Scott and Palmer, the tumor was retropleural, posterior to the lower lobe of the left lung.

Some authors have described this type of tumor as soft, red or brown in color, and encapsulated, whereas others have said that it is firm, nodular and nonencapsulated. Evidently the size, consistency and capsule formation depend, to a large extent, upon the age of the growth and the maturity of its cells.

Diagnosis and Prognosis.—General observation has sustained the claim *that the tumor is radiosensitive, i.e., that sterilization is obtainable even* in the presence of hepatic metastases. The concept that the tumor invariably is fatal within a short period has also been revised. Wyatt and Farber, for instance, reported that 10 of their 40 patients were alive 2 to 5 years after the diagnosis had been made. Wittenberg found that of 73 patients who had been treated by radiation, 22 were still well 3 or more years after having received therapy. Beneventi and Twinem reported the case histories of 10 patients who remained in good health for 3 to 8 years after the discovery of the tumor. Beck and Howard estimated that of 475 cases, 47, or about 10 per cent, were cured.

Ganglioneuroma.—This neurogenous tumor originates from the fully differentiated and mature sympathetic ganglion cells. It may arise in the central, peripheral, sympathetic or parasympathetic systems, as well as *in the medulla of the adrenals*. In most of the reported cases the tumors occurred in the sympathetic chain and were situated in the posterior wall of the abdomen, in the posterior aspect of the pelvis, in the cervical region, and in the *posterior mediastinum*. Of the 90 cases analyzed by James and Curtis, 15 of the tumors originated in the brain, 7 in the cranial nerves, 11 in the neck, 46 in the retroperi-

toneum and 11 in the mediastinum Stout reviewed 220 cases in 1947 and of these 24 tumors had their inception in the neck 134 in the abdomen and 62 in the mediastinum In a report published in 1949 Stout stated that "the most frequent site of involvement (by ganglioneuroma) is the posterior mediastinum"

Pathological Features —As previously mentioned tumors of the sympathetic nervous system are rarely composed of one strain of cells *i e* malignant tumors contain an admixture of fully differentiated cells and



FIG 214 —The histology of ganglioneuroma

benign tumors contain undifferentiated cells This holds particularly true with reference to ganglioneuromas which frequently abound in sympathoblasts On the basis of this observation some pathologists divided the tumors into 3 groups (1) encapsulated tumors which are made up of fully differentiated ganglion cells provided with a stroma that consists of sheathed neurons and collagen (2) tumors made up of mature ganglion cells and scattered immature sympathoblasts and (3) tumors made up of segregated nests of mature ganglion cells and immature sympathoblasts

Mediastinal Ganglioneuromas.—When found in the mediastinum, the ganglioneuroma extends from the bodies of the vertebrae forward and away from the midline, pushing the lungs and pleurae without invading them. The tumor is moderately soft, pale gray, well circumscribed and enveloped by a capsule. In the process of its slow growth, it may attain an enormous size (6 kg), like the giant sarcoma of the pleura. Histologically it is made up of (1) a collection of ganglion cells, *many of which* contain multiple nuclei, (2) foci of calcification and hyalinization, (3) myelinated and nonmyelinated Schwann-sheath proliferations, and (4) areas of cystic degeneration (Fig. 214). In 60 per cent of the cases observed, the patients were under the age of 20. The left side seemed to be involved more frequently.

Illustrative Cases

Case 25. History.—A young man, 18 years old, had apparently enjoyed good health until he was rejected for military service because of an abnormality found in his chest.

Examination revealed a well developed and well-nourished man. The entire right thorax was tympanitic, and the breath sounds were considerably diminished over the right apex anteriorly and the right base posteriorly. There was diminution of fremitus and vocal resonance throughout the whole lung.

Roentgenological Examination.—The apex of the right lung showed a sharply circumscribed area of density, the lower border of which was convex (Fig. 215). A right-anterior, oblique view revealed a mass occupying the posterior portion *of the pulmonary apex. This was confirmed by fluoroscopy.* Examination, following the induction of a pneumothorax, revealed that the mass was outside the lung. There was a slight displacement of the heart and mediastinal structures toward the left. The diagnosis was neurogenic tumor at the apex of the right lung.

Operation.—The tumor in the pleural cavity was seen as an ovoid mass, with its larger pole at the outer extremity and its smaller end lying against the lateral surface of the vertebral bodies. It was situated in the vertebral gutter, lying transversely in front of the second and *third ribs, and reached down* to the fourth rib. It was covered by the posterior parietal pleura. The apex of the upper lobe showed a convex depression that corresponded with the *inferior surface* of the neoplasm, even being equal to it in size.

Pathological Description.—The removed tumor was somewhat egg shaped, encapsulated, and measured 5.5 by 3.6 by 3.8 cm. It was rubbery in consistency and was covered with a smooth capsule, 5 cm in thickness, which was easily stripped from the

tumor to leave a slightly grooved surface On its cut surface the tissue was translucent and pale brown in color On microscopic examination it was found to be a ganglioneuroma

Case 26 History—A 21 year old male suffered from pain under the right shoulder for a period of 4 years The pain was particularly severe on exertion on abrupt motion and after prolonged use of the muscles of the upper back However it was relieved when he lay on his right side and rested his arm in a certain position The tumor had been discovered during his examination for induction into the armed forces



Fig 215—Ganglioneuroma of the right apex Lordotic view

Physical examination showed him to be well developed and well nourished His cardiac vascular and respiratory systems were normal as were the body fluids

Roentgenological examination revealed a rounded mass of homogeneous density about 9 cm in diameter lying laterally to the second third fourth and fifth dorsal vertebral bodies It occupied the upper medial and posterior portions of the right

as seen to be broadly adherent to the vertebral column at the level of the fourth fifth and upper half of the sixth thoracic vertebrae (Fig 217) The lungs showed no disease

Operation —During the operation an elliptical mass extending from the fourth to the seventh ribs and close to the vertebral bodies medially was found in the right vertebral gutter It protruded forward into the pleural cavity for about 6 cm and was densely and partly adherent to the fourth and fifth ribs upon which it rested giving the impression of infiltration It was judged that the growth was malignant and it was removed together with the ribs (Fig 217)



Fig 216 —Ganglioneuroma situated lateral to the upper dorsal vertebrae Pneumothorax demonstrating the extrapulmonary location of the tumor Right and left lateral views

Pathological Report —The specimen consisted of an encapsulated somewhat ovoid mass measuring 6 8 by 7 by 3 5 cm It was grayish white in color smooth elastic and surrounded by a paper thin capsule On its cut surface it was shiny and translucent and had a rather mottled appearance Pieces of two ribs were attached to the growth one piece was attached to the surface and the other was buried in the tumor The tumor was firmly adherent to the periosteum of the rib In the region of the neck of the ribs the tumor had grown between the two ribs and had expanded on the opposite side into an irregular lobulated encapsulated mass which measured 4 by 2 5 by 2 cm The microscopic diagnosis was ganglioneuroma with invasion of the ribs



Fig 217.—Ganglioneuroma. Posterior anterior roentgenological view and the cut surface of the removed tumor.

Diagnosis.—*Localization.*—As a rule intrathoracic neurogenic tumors are located in the upper posterior mediastinum. In fact, whenever a neoplasm is found in the posterior mediastinum it should be considered of neurogenous origin until proven otherwise (Fig. 218).

Age and Sex.—The tumors are encountered in all age groups. Literature abounds in reports of ganglioneuromas that were found in children. However, when they are found in adults, the tumors are more apt to be malignant.



Fig. 218.—Ganglioneuroma in the upper left posterior mediastinum.

Both sexes are about equally affected.

Symptoms.—Unlike the intrapulmonary tumors, the extrapulmonary neurogenic tumors manifest themselves mildly. Following a protracted asymptomatic period, patients begin to complain of either indefinite pains and aches or of tightness and fullness in the chest. Occasionally the pain is radicular. In most cases, as in the illustrative ones presented here, the new

nation of the

location of the

of the superior cervical ganglion reached the area of the tonsil, pushed aside the tongue, and extended up to submaxillary fossa behind the mandible.

When the tumor is in the neck it is located usually between the carotid artery and the jugular vein in front of the vagus nerve. When the upper cervical ganglion is involved, it induces the brachial plexus syndrome.

Dolley and Brewer removed a ganglioneuroma following a preoperative diagnosis of a carcinoma with bronchostenosis. Riggs and Good

observed a patient in whom a ganglioneuroma caused compression and obstruction of the trachea

Pressure on the trachea causes cough dyspnea cyanosis stridor and hoarseness Partial occlusion of the superior vena cava due to pressure induces edema of the upper part of the body cyanosis of the face and dilation of the superficial veins (vena caval syndrome) Pressure on the bronchi interferes with aeration and produces lobar or lobular atelectasis followed by pneumonitis In a case of benign ganglioneuroma removed by Harrington a hemorrhagic pleurisy was found The opinion is that primary nerve tumors of the mediastinum are dangerous The tumors should be removed whenever possible In the material studied by Kent Blades Valle and Graham 41 per cent of cases showed malignant changes

NON NEOPLASTIC MEDIASTINAL LESIONS

The mediastinal space may be the seat of granulomas and of vascular lesions which cast shadows on the x ray films imitating malignant and benign neoplastic diseases The differential diagnosis of these processes is of particular importance from a therapeutic standpoint Some of the lesions most commonly encountered will be briefly described



F c 219—S l tern l th yr l

Substernal Thyroid —Substernal and intrathoracic goiters are extensions of cervical goiters arising from the lower pole of either lobe of the thyroid or from the isthmus of the cervical part of the gland As a t h

Usually substernal goiters cause no symptoms, but at times they will produce substernal distress or a stridor. The diagnosis is arrived at by palpation of the cervical component of the thyroid. In the presence of active thyroid tissue the substernal thyroid can be detected with radioactive iodine.

On x-ray examination the mediastinal mass is visible in the anterior mediastinum continuous with the cervical opacity. It is best visualized by the use of a scanogram. It moves on swallowing. The differential diagnosis between the anteriorly located mediastinal goiter and an anterior mediastinal neoplasm is sometimes difficult. The diagnosis is of therapeutic importance because a substernal thyroid is removed by a thyroidectomy incision, while an upper mediastinal neoplasm requires a thoracotomy.

Aneurysm of the Aorta.—It is generally admitted that the differential diagnosis between a thoracic aneurysm and a neoplasm is frequently not only difficult, but impossible. The theory that the distinction lies in the fact that the aneurysm pulsates while the tumor does not, cannot be relied on. Most of the large aneurysms of the aorta do not pulsate, while some cystic lesions show pulsation because of their proximity to the aorta. Angiocardiography is the method *par excellence* for distinguishing mediastinal lesions of vascular origin from those that are nonvascular, *i.e.*, new growths. By the same method one may ascertain the type of aneurysm, *i.e.*, whether it is saccular or fusiform, also, whether a dilatation of the aorta or a congenital anomaly is involved (Figs. 220 and 221).

Dilatation of the Major Azygos Vein.—The azygos vein arises as the ascending lumbar vein on the right side of the abdomen at the level of the inferior portion of the body of the fourth dorsal vertebra. It rises upward into the thorax along the surfaces of the vertebral bodies to the fourth or fifth thoracic vertebra. It then changes its course anteriorly and inferiorly, and to the left to enter the superior vena cava. (The major azygos vein acts as a manometer signaling the pressure in the vena cava.)

When the terminal segment of the azygos vein becomes dilated it simulates a mediastinal tumor. Fluoroscopy during the performance of the Valsalva maneuver is believed to be the method most suitable for the determination of the vascular nature of the shadow.

Aneurysm of the Innominate Artery.—Aneurysmal dilatation of the innominate artery occurs chiefly in persons suffering from syphilis with a concomitant luetic aortitis. Arteriosclerosis is very rarely complicated by an aneurysm of the innominate artery. The condition has also been found in coarctation of the aorta. Innominate-artery aneurysm is a serious disease which may cause death by asphyxiation induced by tracheal compression. Vascular compression results in venous conges-



Fig 220—Aneurysm of the aorta

Fig 221—Aneurysm of the aorta posteroanterior and lateral views

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Chapter 20

Cysts

THE lungs are the seat of a variety of cysts that are of interest *per se* and important in differential diagnosis from tumors These cysts are classifiable according to pathogenesis structure and location Currently they are differentiated into (1) congenital or developmental resulting from a maldevelopment *in utero* and (2) acquired (in early childhood or later in life) Congenital cysts are further divided into (1) bronchogenic type and (2) alveolar type (balloon cysts pneumocele) both of which may be either solitary or multiple The former may contain pus blood and clear fluid and may or may not contain air The latter always contains air

CONGENITAL CYSTS

Bronchiogenic Cyst —The bronchiogenic cyst is the result of an anomalous development of the lung anlage it is found in the lung and also in the mediastinum Histologically it is made up of a wall which contains almost all the elements of the normal bronchus namely smooth muscle fibers elastic tissue cartilage mucous glands and lymphoid tissue The wall is lined by ciliated columnar epithelium or by cuboidal epithelium

The bronchiogenic cyst (Fig 224 and 225) is usually round or oval and may be unilocular or multilocular It has a smooth surface varies in size from 2 to 10 cm and contains an odorless viscid or milky substance which may become brownish due to hemolyzed blood Generally it is located in (1) the upper part of the posterior mediastinum (2) the neighborhood of the trachea (at the bifurcation) or (3) the right border of the esophagus Occasionally it is found attached to the carina by a stalk A bronchiogenic cyst in the lingula is demonstrated in Figure 226

Paratracheal cysts have been found chiefly on the right side of the chest the larger ones usually located beneath the pleura the smaller ones within the pulmonary parenchyma Often they occupy a high paratracheal position or are located at the hilus A considerable number of cysts has been found situated along the course of the esophagus Some were embedded in the esophageal wall

Mediastinal cysts are solitary (rarely multiple) while the parenchymal cysts are small and generally multiple As a rule parenchymal cysts are



Fig 224.—Bronchiogenic cyst in a male of 17. Asymptomatic. Histologically the wall was found to be lined with respiratory epithelium and the cavity contained sterile mucoid fluid. The fluid level is indicated by arrows.



Fig 225.—Bronchiogenic cyst another aspect

lodged in the upper lobes a fact which is important in differential diagnosis The roentgenological picture of scattered (parenchymal) cysts resembles the picture of multiple bronchiectasis but bronchiectasis is usually confined to the lower lobes



Fig 226—Bronchogenic cyst of lingula in a male aged 50 (arrow) Asymptomatic Lingulectomy Histological finding of an epithelial lined cyst

There seems to be a difference of opinion as to whether under normal conditions there is communication between the bronchogenic cyst and the bronchus Adams and Thornton have stated that there is "no connection with the bronchi" and Lapply too affirmed that "typically the cyst does not communicate with the trachea or the bronchi" However Blades stated that "a lumen communicating with the trachea or the bronchus can usually be demonstrated"

Sex—Age—Bronchiogenic cysts occur at all age periods and affect both sexes *with almost equal frequency*. They are also found in stillborn fetuses which is additional evidence of their congenital origin.

Clinical Manifestations—A cyst may be present in the mediastinum or in the pulmonary parenchyma *without producing symptoms*. In adults it is either accidentally discovered at a routine roentgenological examination or unexpectedly at autopsy. On the other hand symptoms may appear early in life. As with other benign lesions of the lungs the symptoms often depend upon the size and location of the cyst. Mediastinal cysts are mostly asymptomatic. Symptoms appear as a result of the compression of a bronchus. This causes bronchostenosis and atelectasis of the lung *which in turn induce respiratory distress* (dyspnea, cyanosis or cough). The complaints most frequently occurring are attacks of dizziness, easy fatigability, pain in the chest and wheezing. These symptoms are usually precipitated by an infection of the contents of the cyst and also by hemorrhage. Such an infection rarely occurs by way of the blood stream as *some observers have postulated*; rather it occurs either by way of the bronchus (most cysts communicate with one or several bronchi) or by contiguity from a pericystic pneumonitis. By compressing the pulmonary parenchyma the expanding cyst renders it vulnerable to infection. Bronchiogenic cysts bleed readily and are apt to perforate and pour out their contents into the pleural cavity. In children the occurrence of intracystic tension is one of the first and most alarming symptoms.

On roentgenological examination *the solitary cyst is seen as a round* or oval opacity in front of the vertebral bodies. Its position in the posterior mediastinal space precludes the possibility of its being mistaken for a thymogenic tumor, a terato dermoid or a mesothelial cyst, all of which are located in the anterior mediastinal space. Nor can it be taken *for a lymphoma since lymphomas are confined predominantly* to the middle mediastinum. Bronchiogenic cysts have however been mistaken for tuberculous cavities, pulmonary abscesses, empyemas, hiatus hernias and bronchiogenic carcinomas. But *when a thick walled* cavitary lesion containing a fluid level is discovered, a bronchiogenic cyst should always be suspected.

Congenital Bronchiectasis *(Fig. 227)*—Another variety of congenital cystic disease is the so called congenital bronchiectasis. This is believed to result from *blockage of the lumina of the bronchial* buds in the embryo which eventually develop single or multiple cystic cavities structurally imitating the pattern of the bronchus (*i.e.* including cartilage, mucous glands and epithelial lining). According to Norris and Tyson the original defect consists of a small irregular dilatation of the smaller *bronchioles*. When arrested in this stage the dilatation results in fetal or cystic bronchiectasis *characterized by uniform sized* thin walled cysts

in the terminal arborization of the bronchial tree If the process continues these bronchiolar dilatations are pinched off up to several centimeters in diameter from larger cysts When the process is diffuse it gives rise to the honeycomb lung

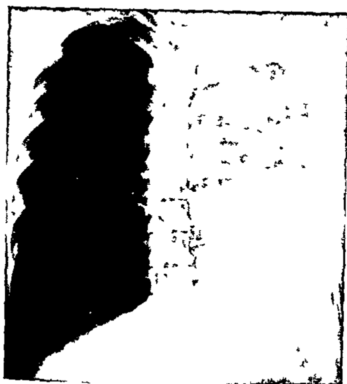


Fig 227—Congenital bronchiectasis in a white female of 41 with life long cough productive of 1 to 2 cups of yellow green sputum Repeated respiratory infections No bronchial stenosis on bronchoscopy Pneumonectomy disclosure of large cystic ectatic bronchi Vanished lung Postoperative cure

The congenital origin of these cysts is indicated by their location in the upper lobe of the lung by lack of anthracotic pigmentation in the involved portion of the lung by wide communication with the bronchi and finally by the relatively mild inflammatory changes in contrast to those present in acquired bronchiectasis of a quasi similar extent In many cases the symptoms can be traced to early childhood

The cysts have a tendency to become infected either through a bronchial communication or from an infected lung

Usually the picture is that of a cluster of thin walled closely packed round or oval cavities of variable size which communicate with the bronchial branches and sometimes with each other and which may have one or more lobes (Fig 227)

Interlobar Bronchopulmonary Sequestration—A striking example of cyst formation caused by an embryonic maldevelopment is the so called "interlobar bronchopulmonary sequestration" in which the lower lobe of the lung is partially or completely dislocated or sequestered (*in utero*) from the normal blood supply The sequestered segment is supplied



Fig 228—Intralobar sequestration Posteroanterior and lateral views The fluid level is indicated by arrow Male of 36 complaining of cough fever and hemoptysis Right lower lobectomy with disclosure of an infected thick walled cyst A large systemic artery entered the cyst from below the diaphragm

by an anomalous artery which arises from the thoracic aorta just above or just below the diaphragm The artery pierces the inferior pulmonary ligament and enters the sequestered lobe The venous drainage is effected by way of the normal pulmonary vein

The sequestered lobe contains dilated (*i e* bronchiectatic) bronchi running parallel to the anomalous artery embedded in fetal lung tissue and one or several thin walled bronchiogenic cysts Usually the sequestered segment has no connection with the rest of the bronchial tree and when a connection is present it is very small A solitary cyst is discernible by the presence of a fluid level (Fig 228), while mucoid

matter is found in cases of multiple cysts. The cysts show expansible characteristics incident to infection or to bronchial occlusion. Histologically they are similar to bronchogenic cysts.

On x-ray examination the sequestered lobe is seen as a circumscribed triangular area of density confined to the lower lobe and containing one or several thin-walled cysts. The lesion is particularly well visualized by laminagraphy and by a swallow of barium. In some cases the differential diagnosis between intralobar bronchopulmonary sequestration, suppurative bronchiectasis and diaphragmatic hernia may require a bronchographic study. The anomaly is sometimes found to coexist with a diaphragmatic hernia or with an arteriovenous fistula.

The condition may remain asymptomatic. Symptoms are caused by the infection of the sequestered lobe from the adjacent lung. Patients complain of recurrent attacks of "colds" accompanied by low grade fever, chills and cough productive of a mucoid sputum which is sometimes blood streaked. On physical examination the signs are compatible with consolidation of the lower lobe. Indeed the finding in young adults of a rather well delineated area of density in the posterior basal segment of the lower lobe (the left side is affected predominantly) should suggest the possibility of an intralobar bronchopulmonary sequestration.

The treatment consists in the surgical removal of the sequestered part of the lung.

Gastroenteric.—Like the bronchogenic cysts, gastroenteric cysts are situated paravertebrally in the posterior mediastinal space. They lie close to the root of the lung and extend retropleurally, mainly to the right side. It has been estimated that about one sixth of them are confined to the center of the thorax, one fourth to the left hemithorax and the remaining number to the right hemithorax.

The gastroenteric cyst is pear- or oval-shaped and varies in size from 2 to 15 cm in diameter. It may contain but a few or as much as 400 cc of clear, amber, milky or brown fluid which often contains hydrochloric acid and pepsin. The cyst is unilocular and is firmly adherent to the adjacent structures, i.e., to the esophagus and the lung. It communicates with a bronchus.

[illegible]

cells secrete hydrochloric acid and pepsin mentioned above. The wall contains a muscularis mucosa, a submucosa, and circular and longitudinal muscular layers. (There are cases on record where the mucosa of the cyst contained a peptic ulcer. An instance of cancer has also been reported.)

This type of cyst is congenital and some observers believe it represents an intrathoracic vestige of the vitelline sac; others believe it is the out

come of an outpocketing of epithelial nodules capable of producing a gastric mucosa. Like the bronchiogenic cyst, the gastroenteric cyst is frequently accompanied by maldevelopments in other parts of the body, namely, *spina bifida, scoliosis, diverticula, and abdominal enteric cysts*. Although in most cases these cysts are lined by a mucosa of the gastric type, some with enteric linings have been observed (the so-called "enterocystomas"). They are found only in adults and are situated in the region of the lower half of the esophagus between the muscular layers to which they are attached. Gastroenteric cysts resemble bronchiogenic cysts but contain no cartilage in the walls.

Clinical Manifestations.—While small cysts produce no symptoms, large ones induce an array of symptoms that resemble inflammatory and neoplastic processes of the lungs. By compressing the bronchus, they produce bronchostenosis and obstructive pneumonitis, and by compressing the trachea, they cause dysphagia. Occasionally they displace the heart and lead to the formation of a scoliosis.

Patients generally suffer from a persistent cough, frequent "colds," pain in the chest, and, occasionally, hemoptysis. About one-fourth have attacks of suffocation. The symptoms produced by the gastroenteric cyst are not specific and often depend upon the organ involved.

In about 75 per cent of cases the symptoms appear in the first year of life. In children the cyst is mistaken for lymphomatoid disease or a neurogenic tumor; in adults it is mistaken for a primary or metastatic neoplasm.

The diagnosis is often arrived at after a thorough clinical and laboratory investigation. Aspiration of fluid from the cyst (which, as mentioned, contains hydrochloric acid and pepsin), is, indeed, the "acid test" that establishes the diagnosis.

PERICARDIAL COELOMIC*

Structure.—The wall of the pericardial cyst is made up of a thin layer of connective tissue containing a few blood vessels, capillaries, and adipose tissue. *When the cyst is distended, the cells of the mucosa resemble endothelial cells; when it is not distended, they resemble cuboidal mesothelial cells.* As a rule, the cyst contains a clear, spring-water fluid with a low specific gravity and traces of protein, but, occasionally the contents are turbid and sanguineous.

The pear-shaped cyst is attached to the parietal pericardium by a pedicle and bulges into the thoracic cavity. Various sizes have been described. The largest that has been reported was about 6 cm. in diameter.

*Also known as serosal cysts, simple mesothelial cysts and mediastinal mesothelial cysts of the pericardium.

Unlike bronchiogenic and gastroenteric cysts which are located in the posterior mediastinum pericardial coelomic cysts are found in the anterior mediastinum in contact with the chest wall In Lamberts cases they were found in various locations *viz* lying on the thoracic wall, on the diaphragm on the pericardium (Fig 229) and in the lingula of the left lung In most instances they were found close to the diaphragm in the right cardiophrenic angle

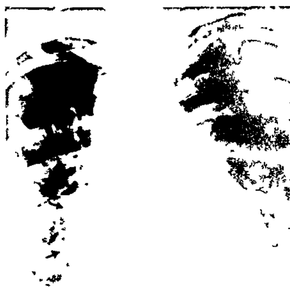


Fig 229—Pericardial coelomic cyst in a woman operated on for a fibrous mesothelioma of the pleura Incidental finding during surgical intervention

Pathogenesis—According to Lambert the pericardial cyst is a mal development that reverts to the earlier stages of organogenesis when the so-called "pericardial coelom is being formed from a fusion of the mesenchymal lacunae In his opinion the failure of one of the primitive lacunae to merge with others eventually results in the formation of an independent cavity *i e*, in the production of the postembryonic pericardial cyst Other writers have stated that the cyst may arise from the pericardium itself

Age–Sex—The pericardial coelomic cyst has been found in persons of various age groups (In one case it was discovered in a woman 86 years old) Both sexes are equally affected

scattered throughout the organ Oswald and Parkinson (the first to give a comprehensive account of the condition) found several of their cases in patients with xanthomatosis, tuberous sclerosis, hepatic diseases, and pituitary abnormalities Other observers have noticed honeycomb lung in Hand-Schuller-Christian disease, and in eosinophilic granuloma, and the *x*-ray picture shown in Figure 230 demonstrates a case of honey



comb lung in a 6-year-old white male child with Letterer Siwe disease The child was subjected to repeated attacks of bilateral pneumothorax and suffered from a progressive dyspnea He died in respiratory failure The diagnosis was made by means of a biopsy of a cervical lymph node The left lung showed scattered minute granulomas and the right lung showed a pneumothorax and a characteristic picture of a honeycomb lung

It is almost universally accepted that such cysts are acquired postpartum, but the mechanism of their production is debatable

The etiology of Letterer-Siwe disease, Hand Schuller-Christian disease, and eosinophilic granuloma is unknown The abnormality in each case consists in the excessive proliferation of cells of the reticuloendothe-

lial system (i e histiocytes macrophages) This proliferation is particularly prominent in organs normally rich in these cells viz lymph nodes spleen and bone marrow, and has also been observed in the skin and in the lungs In Hand Schuller Christian disease these cells are loaded with lipids (i e lipid histiocytosis) in Letterer Siwe disease they are lipid free (i e nonlipid histiocytosis) while in eosinophilic granuloma the picture is dominated by eosinophiles One school of investigators regards each disease as an independent entity another school considers the three diseases (referred to as "histiocytosis X") as different stages of the same disorder They stated for example that Letterer Siwe disease is but an acute form of eosinophilic granuloma The two concepts cannot be adequately discussed here It is well to point out that in all of these conditions the histological process consists of a granuloma which is by no means specific It is usually disseminated with about equal density throughout one or both lungs The granulomas eventually become fibrosed It is believed that the ensuing cysts are related to the fibrosis It is said that they begin to form in areas where the granulomas and the fibrosis are most conspicuous the fibrosis eventually leading to obliteration of particular segments of the airway with the formation of cysts

The problem requires further study

ADDENDUM

ECHINOCOCCUS CYST

The Parasite—The parasite *(Taenia echinococcus)* that causes this disease is a cestode tapeworm measuring 4 mm in length and consisting of a head (scolice) a neck and two body segments The terminal segment is the site of ovulation The larval cyst inhabits sheep or swine (rarely man) who are the intermediate hosts while the mature cyst thrives in dogs (or wolves) who are the definite hosts The dog becomes infected by feeding on the flesh of sheep who harbor the parasite while man contracts the disease by contamination from the dog

Propagation—Once in the body the adult worm attaches itself to the gastric or the upper intestinal mucosa by means of four suckers that are provided with numerous hooklets It penetrates the portal circulation and the liver (the most common site of the disease) or the lungs (the site next in frequency) Other organs such as the brain the bones the pericardium and the pleura are rarely involved

The cyst—The hydatid cyst or developing embryo consists of three layers

1 The endocyst or innermost layer is the germinal focus The inner surface of this focus generates the brood capsules with their scolices it

also secretes the clear watery fluid of the cyst The fluid which is alkaline or neutral and has a specific gravity of about 1 015 contains the brood capsules and the scolices It is antigenic

2 *The ectocyst* which is formed by the secretions of the germinal layer is a laminated membrane that envelops the endocyst

3 *The pericyst* which *is made up of collagenic fibers* and has a tendency to grow in thickness *with age is formed by the host* and is not organically related to the hydatid cyst



Fig 231 —Echinococcus cyst of the lung posteroanterior and lateral views

Intrapulmonary Cyst —As a rule the lungs harbor a single cyst (Fig 231) *When several cysts are present in all likelihood they* have resulted from a "massive" infection or from the dissemination of a complicated hepatic cyst

The cyst is usually enclosed within the pulmonary parenchyma It occurs more often in the right than in the left lung, but has no predilection for lobe *It fits snugly into the surrounding* tissue and can be enucleated *in toto* with relatively little difficulty *It grows* at a slow pace In fact in localities *where the disease is prevalent it has been* found that even though contaminations have occurred during childhood manifestations do not appear until puberty or later The reaction caused around the cyst is slight or else it consists of a moderate pneumonitis and a pericystic atelectasis of the pulmonary tissue Pressure on bone *or blood vessels may produce erosion* of these structures

Clinical Manifestations —An intact cyst (simple) remains asymptomatic Only when it is of considerable size (*some cysts become so* large as to contain a quart or more of fluid) is it apt to displace the

mediastinal contents reduce the respiratory surface of the lung and induce dyspnea cough pain tightness of the chest and an occasional effusion into the pleural cavity Symptoms make their appearance either when the cyst is traumatized or when it becomes infected Indeed, even in such instances the broken cyst may evacuate its contents as well as its wall through the bronchus and thus bring about a cure However it is also possible that when a tear occurs in the cyst the brood capsules and the scolices contained in the fluid may make their way into the lung where they set up new colonies of parasites and produce a pneumonitis and a suppuration The wall of the cyst may lodge in the trachea and cause asphyxia

The wall of the apparently impermeable cyst is evidently porous as it allows imperceptible quantities of fluid to pass through the "pores" and steadily sensitize the host If fluid subsequently escapes from a ruptured cyst (as a result of a surgical or other kind of trauma) it will induce an anaphylactic shock which may be fatal In the process of removing a hydatid cyst surgeons take precautions against spilling its contents into the surrounding tissues Nonfatal allergic manifestations are the appearance of urticaria rashes pruritus and asthmatic attacks

Rupture of the cyst into the pleural cavity with the resultant outpouring of considerable quantities of fluid induces pneumothorax pyopneumothorax or empyema

A cyst that lies astride a bronchus may erode its wall Barrett and Thomas stated that even after the removal of a large parasite from a lung it is unusual to find large bronchial fistulas communicating with the empty space As a rule there are one or two small fistulous communications Hemoptyses which occur in many cases are probably caused by the rupture of anastomoses between the bronchial and the pulmonary arterial radicles around the cyst

Diagnosis—None of the stages through which the disease passes reveal characteristic symptoms Elaborate roentgenological and laboratory investigations are required in order to make a diagnosis

Roentgenological Examination—The x ray appearance depends upon whether the cyst is a simple one i e nonruptured and noninfected or whether it is infected and disintegrating The simple cyst is usually seen as a round or oval shadow with clear cut edges surrounded by a quasi normal pulmonary parenchyma If the wall meets resistance the shadow may show indentations The edges are often irregular in cysts of long standing In the lungs the adventitia probably never shows calcification In the liver however calcification of the adventitia is frequently found

Both Escudero and Nemenov independently observed that the cyst may change its shape during respiratory movements (the E

Nemenov sign) Large cysts may displace the mediastinal contents and produce bulging of the ipsilateral hemithorax in younger patients

When the cyst becomes enlarged, a communication with the bronchi may be established Upon coughing air will penetrate between the pericyst (adventitia) and the ectocyst, producing a semilunar image, or an air cap (*calotte aerienne*) This is usually a sign of disintegration, *i e*, rupture and evacuation of the fluid and the membrane via the bronchus As a rule this is accompanied by an infection of the cyst causing a pyopneumocyst At this stage, the disease resembles a putrid lung abscess

The shadow cast by a simple cyst may be confused with either a benign tumor, a terato dermoid an aneurysm of the aorta, or even a bronchiogenic cancer

Laboratory Tests —The biological tests currently used are

1 The intradermal Cassoni test, which is equivalent to the Mantoux tuberculin test The steady leakage of fluid from the cyst creates a state of hyperergy, which can be detected by the intradermal injection of minute quantities of hydatid fluid This can be obtained from an uncomplicated cyst of a sheep In order to avoid a severe allergic reaction the initial dose of the injected antigen should be small

2 The complement fixation test of Weinberg which is equivalent to the complement fixation test in syphilis Human serum supposedly containing hydatid antibodies is put in contact with the antigen *present in the fluid obtained from* a cyst of a sheep The Cassoni test yields a higher percentage of positive results than the Weinberg test Only positive results should be taken into consideration

When the cyst is a complicated one, examination of the sputum for hooklets and scolices may lead to a correct diagnosis In instances of rupture of the cyst into the pleural cavity, the pleural exudate should be studied diligently *Needless to say, puncturing of the cyst for* diagnostic purposes is prohibited As in other parasitic diseases the blood often shows eosinophilia

In case of failure to arrive at a *diagnosis by laboratory tests, an* exploratory thoracotomy should be resorted to

Treatment —Therapy consists in surgical extirpation of the cyst

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Chapter 21

Radiographic Diagnosis

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The great variety of lesions encountered in the mediastinal space (i.e., primary and secondary, benign and malignant, granulomatous and cystic) require the acumen of the observer in addition to the use of technical diagnostic procedures.

Generally it is well to be guided by *the observation that benign* lesions occur mostly in younger persons and are frequently discovered on a routine roentgenological examination. In order to arrive at an x-ray diagnosis of a mediastinal lesion, it is of importance to ascertain:

1. The exact site of the lesion.
2. The gross appearance of the lesion, i.e., its shape, size, margins, density, and the presence or absence of calcification.
3. The involvement of the *mediastinal structures by the lesion*, and whether these structures are mobile or fixed.
4. The involvement of the adjacent bones of the thoracic cage.
5. Whether the lesion is primary or metastatic.

Site of Lesion.—The exact location of an abnormal tumefaction *within the mediastinum is often of considerable assistance in the* differential diagnosis. Many lesions show a predilection for certain locations. In order to determine location, fluoroscopy and films in frontal, lateral, and oblique views are necessary; occasionally tomography may be required. The site is particularly helpful in the diagnosis of a pericardial coelomic cyst, a diaphragmatic hernia (through the foramen of Morgagni), a thymoma, an intrathoracic goiter, and tumors of neurogenic origin. *Benign tumors and cysts are usually observed* projecting from only one side of the mediastinum, while malignant tumors and lymph-node enlargements may widen one or both sides of the mediastinum.

Two conditions, not truly mediastinal in location, and which may be confused with substernal goiter, are occasionally found in the region of the thoracic inlet: (1) a large cricopharyngeous diverticulum (Zenker), *which may project into the thoracic inlet* from the base of the neck. Barium opacification of the esophagus readily establishes the diagnosis; (2) a tortuosity or aneurysmal dilatation of the innominate

and the subclavian arteries. These round densities at the thoracic apex are always seen on one side, usually on the right side. They pulsate intrinsically, do not displace the trachea and may contain vascular calcifications. They are observed in older individuals, often along with hypertension and calcific arteriosclerosis.

Appearance.—An appreciation of the exact appearance of the mediastinal enlargement will often furnish important clues as to the identity of the lesion. To get this information usually requires Bucky and tomographic studies in addition to the routine radiographic and fluoroscopic examinations. To demonstrate diaphragmatic hernia a barium meal and barium enema examinations are required in cases of basilar densities adjacent to the diaphragm.

Although there are many exceptions, benign tumors are usually smaller than either malignant tumors or collections of enlarged mediastinal lymph nodes. Also benign tumors are very slow growing and the cysts generally stop growing after they have attained certain sizes. In these cases it is important for differentiation to review all available films taken previously. A change in size during respiration may be seen fluoroscopically in some cases of pericardial coelomic cyst and when observed a diagnosis of cyst is strongly suggested.

Shape.—The shape of the density is also of importance. Cysts and small benign tumors often demonstrate a single ovoid or semilunar curve. On the other hand malignant tumors or enlarged lymph nodes usually show more complex shapes with multicrescentric, undulating or irregularly straightened margins (due to irregularities of tumor growth or fusion of the adjacent lymph node masses). The border of benign tumors and cysts remains sharply defined and smooth while the margins of malignant tumors, lymph node metastases or lymphoblastomas tend to become hazy, ill defined and infiltrative as the disease progresses.

The mediastinal densities are usually of uniform density. They may however contain areas of calcification which are most frequently encountered in (1) tuberculous lymph nodes, (2) intrathoracic thyroid tumors, (3) thymic tumors and cysts, (4) dermoid cysts and (5) certain tumors of neurogenic and connective tissue origin.

Mobility.—The determination of mediastinal mobility is of considerable importance in evaluating the nature and extent of tumors in this region. Benign neoplasms, cysts, lymphoblastomas in the early stages and most inflammatory lymph nodes do not impair the mobility of the mediastinal structures. On the other hand infiltrating carcinomas, advanced inflammatory processes or Hodgkin's disease do restrict mediastinal motion.

Mobility of the mediastinum is studied fluoroscopically and radiographically. Fluoroscopically the degree of respiratory deviation of the mediastinum to the right or to the left is noted. The radiographic investigation is more important and includes frontal studies made with the

patient in the right and left lateral recumbent positions When mobile, the mediastinum will move toward the dependent side At times, the mediastinal mobility may be better appreciated by including lateral recumbent films made in deep inspiration and expiration

Invasion —Evidence of invasion of mediastinal structures is of great value in determining the nature and extent of mediastinal involvement This has been described in the section on pulmonary neoplasms

Bony Cage —Investigation of the mediastinum must also include a study of the adjacent thoracic bony cage Most important are the heads and the medial posterior portions of the ribs, as well as the vertebral bodies and the transverse processes Studies of the sternum are of importance in anterior mediastinal lesions Special "spot" Bucky films and tomography may be required to demonstrate involvement of these areas, and should be obtained where indicated In cases of benign tumors of neurogenic origin which lie in the posterior mediastinum, there is the possibility of pressure erosion upon the ribs or the vertebral bodies *Pathognomonic of the hourglass neurogenic tumor is a combination of* enlarged unilateral intervertebral foramen and widening of the space between the heads of the adjacent ribs in the involved area Frequently there are pressure erosions upon these ribs locally Certain mediastinal malignancies, on the other hand, *invade the bodies of the adjacent thoracic* vertebrae by contiguity and cause irregular bony destruction In Hodgkin s disease involving the anterior mediastinum it is not uncommon to find evidence of invasion of the sternum Similarly, sternal invasion is not rare in cases of carcinoma of the breast either prior to mastectomy or postoperatively

Primary Source —Of great importance in the study of mediastinal masses is the search for a possible primary malignant neoplasm elsewhere, since metastatic lymph-node involvement is one of the most common causes of mediastinal enlargement The common primary sites, *i e*, the breast the esophagus, the lungs and the stomach, should be carefully explored

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